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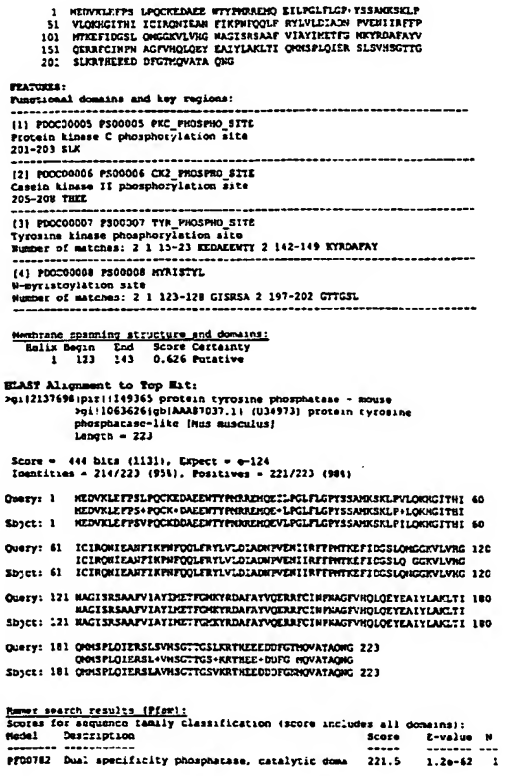
[Continued on next page]

(54) Title: ISOLATED HUMAN PHOSPHATASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN PHOSPHATASE PROTEINS, AND USES THEREOF



```
  1  MEDVKLEFPS LPQCKEDAEE WTYPMRREMQ EILPGLFLGP YSSAMKSKLP
 51  VLQKMGITHI ICIRQNIEAN FIKPNFQQLF RYLVLDIADN PVENIIRFFP
101  MTKEFIDGSL QMGGKVLVHC WAGISRSAAF VIAYIMETFG MKYRDAFAYV
151  QERRFCINPN AGFVHQLQEY EAIYLAKLTI QMMSPLQIER SLSVHSGTTG
201  SLKRTHEEED DFGTMQVATA QMG

FEATURES:
Functional domains and key regions:
---------------------------------------------------------------------
(1) PDOC00005 PS00005 PKC_PHOSPHO_SITE
Protein kinase C phosphorylation site
201-203 SLK
---------------------------------------------------------------------
(2) PDOC00006 PS00006 CK2_PHOSPHO_SITE
Casein kinase II phosphorylation site
205-208 THEE
---------------------------------------------------------------------
(3) PDOC00007 PS00007 TYR_PHOSPHO_SITE
Tyrosine kinase phosphorylation site
Number of matches: 2 1 15-23 KEDAEEWTY 2 142-149 KYRDAFAY
---------------------------------------------------------------------
(4) PDOC00008 PS00008 MYRISTYL
N-myristoylation site
Number of matches: 2 1 123-128 GISRSA 2 197-202 GTTGSL
---------------------------------------------------------------------

Membrane spanning structure and domains:
  Helix Begin   End   Score Certainty
      1   123   143   0.626 Putative

BLAST Alignment to Top Hit:
>gi|2137698|pir||I49365 protein tyrosine phosphatase - mouse
          >gi|1063626|gb|AAA87037.1| (U34973) protein tyrosine
          phosphatase-like [Mus musculus]
          Length = 223

 Score =  444 bits (1131), Expect = e-124
 Identities = 214/223 (95%), Positives = 221/223 (98%)

Query: 1   MEDVKLEFPSLPQCKEDAEEWTYPMRREMQEILPGLFLGPYSSAMKSKLPVLQKMGITHI 60
            MEDVKLEFPS+PQCK+DAEEWTYPMRREMQE+LPGLFLGPYSSAMKSKLP+LQKMGITHI
Sbjct: 1   MEDVKLEFPSVPQCKDDAEEWTYPMRREMQEVLPGLFLGPYSSAMKSKLPILQKMGITHI 60

Query: 61  ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQMGGKVLVHC 120
            ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQMGGKVLVHC
Sbjct: 61  ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQMGGKVLVHC 120

Query: 121 WAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI 180
            WAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI
Sbjct: 121 WAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI 180

Query: 181 QMMSPLQIERSLSVHSGTTGSLKRTHEEEDDFGTMQVATAQMG 223
            QMMSPLQIERSL+VHSGTTGS+KRTHEE+DDFG MQVATAQMG
Sbjct: 181 QMMSPLQIERSLAVHSGTTGSVKRTHEEDDDFGRMQVATAQMG 223

Pfscan search results (Pfam):
Scores for sequence family classification (score includes all domains):
Model    Description                                Score    E-value  N
-------- -----------                                -----    -------  ---
PF00782  Dual specificity phosphatase, catalytic doma  221.5    1.2e-62  1
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(57) Abstract: The present invention provides amino acid sequences of peptides that are encoded by genes within the human genome, the phosphatase peptides of the present invention. The present invention specifically provides isolated peptide and nucleic acid molecules, methods of identifying orthologs and paralogs of the phosphatase peptides, and methods of identifying modulators of the phosphatase peptides.

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ISOLATED HUMAN PHOSPHATASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN PHOSPHATASE PROTEINS, AND USES THEREOF

RELATED APPLICATIONS

The present application claims priority to provisional application U.S. Serial No. 60/182,194, filed February 14, 2000 (Atty. Docket CL000259-PROV) and U.S. Serial No. 09/685,853, filed October 11, 2000 (Atty. Docket CL000871).

FIELD OF THE INVENTION

The present invention is in the field of phosphatase proteins that are related to the protein tyrosine phosphatase subfamily, recombinant DNA molecules and protein production. The present invention specifically provides novel protein tyrosine phosphatase peptides and proteins and nucleic acid molecules encoding such peptide and protein molecules, all of which are useful in the development of human therapeutics and diagnostic compositions and methods.

BACKGROUND OF THE INVENTION

Phosphatase proteins, especially the member of protein tyrosine phosphatase subfamily, are a major target for drug action and development. Accordingly, it is valuable to the field of pharmaceutical development to identify and characterize previously unknown members protein tyrosine phosphatase subfamily. The present invention advances the state of the art by providing a previously unidentified human phosphatase proteins that have homology to members of the protein tyrosine phosphatase subfamily.

Protein Phosphatase

Cellular signal transduction is a fundamental mechanism whereby external stimuli that regulate diverse cellular processes are relayed to the interior of cells. The biochemical pathways through which signals are transmitted within cells comprise a circuitry of directly or functionally connected interactive proteins. One of the key biochemical mechanisms of signal transduction involves the reversible phosphorylation of certain residues on proteins. The phosphorylation state of a protein may affect its conformation and/or enzymic activity as

well as its cellular location. The phosphorylation state of a protein is modified through the reciprocal actions of protein phosphatases (PKs) and protein phosphatases (PPs) at various specific amino acid residues.

Protein phosphorylation is the ubiquitous strategy used to control the activities of eukaryotic cells. It is estimated that 10% of the proteins active in a typical mammalian cell are phosphorylated. The high-energy phosphate that confers activation and is transferred from adenosine triphosphate molecules to protein-by-protein phosphatases is subsequently removed from the protein-by-protein phosphatases. In this way, the phosphatases control most cellular signaling events that regulate cell growth and differentiation, cell-to-cell contacts, the cell cycle, and oncogenesis.

The protein phosphorylation/dephosphorylation cycle is one of the major regulatory mechanisms employed by eukaryotic cells to control cellular activities. It is estimated that more than 10% of the active proteins in a typical mammalian cell are phosphorylated. During protein phosphorylation/dephosphorylation, phosphate groups are transferred from adenosine triphosphate molecules to protein-by-protein phosphatases and are removed from the protein-by-protein phosphatases.

Protein phosphatases function in cellular signaling events that regulate cell growth and differentiation, cell-to-cell contacts, the cell cycle, and oncogenesis. Three protein phosphatase families have been identified as evolutionarily distinct. These include the serine/threonine phosphatases, the protein tyrosine phosphatases, and the acid/alkaline phosphatases (Carbonneau H. and Tonks N. K. (1992) Annu. Rev. Cell Biol. 8:463-93).

The serine/threonine phosphatases are either cytosolic or associated with a receptor. On the basis of their sensitivity to two thermostable proteins, inhibitors 1 and 2, and their divalent cation requirements, the serine/threonine phosphatases can be separated into four distinct groups, PP-I, PP-IIA, PP-IIB, and PP-IIC.

PP-I dephosphorylates many of the proteins phosphorylated by cylic AMP-dependent protein phosphatase and is therefore an important regulator of many cyclic AMP mediated, hormone responses in cells. PP-IIA has broad specificity for control of cell cycle, growth and proliferation, and DNA replication and is the main phosphatase responsible for reversing the phosphorylations of serine/threonine phosphatases. PP-IIB, or calcineurin (Cn), is a Ca.sup.+2 -activated phosphatase; it is involved in the regulation of such diverse cellular functions as ion channel regulation, neuronal transmission, gene transcription, muscle glycogen metabolism, and lymphocyte activation.

PP-IIC is a Mg.sup.++ -dependent phosphatase which participates in a wide variety of functions including regulating cyclic AMP-activated protein-phosphatase activity, Ca.sup.++ -dependent signal transduction, tRNA splicing, and signal transmission related to heat shock responses. PP-IIC is a monomeric protein with a molecular mass of about 40-45 kDa. One .alpha. and several .beta. isoforms of PP-IIC have been identified (Wenk, J. et al. (1992) FEBS Lett. 297: 135-138; Terasawa, T. et al. (1993) Arch. Biochem. Biophys. 307: 342-349; and Kato, S. et al. (1995) Arch. Biochem. Biophys. 318: 387-393).

The levels of protein phosphorylation required for normal cell growth and differentiation at any time are achieved through the coordinated action of PKs and PPS. Depending on the cellular context, these two types of enzymes may either antagonize or cooperate with each other during signal transduction. An imbalance between these enzymes may impair normal cell functions leading to metabolic disorders and cellular transformation.

For example, insulin binding to the insulin receptor, which is a PTK, triggers a variety of metabolic and growth promoting effects such as glucose transport, biosynthesis of glycogen and fats, DNA synthesis, cell division and differentiation. Diabetes mellitus, which is characterized by insufficient or a lack of insulin signal transduction, can be caused by any abnormality at any step along the insulin signaling pathway. (Olefsky, 1988, in "Cecil Textbook of Medicine," 18th Ed., 2:1360-81).

It is also well known, for example, that the overexpression of PTKs, such as HER2, can play a decisive role in the development of cancer (Slamon et al., 1987, Science 235:77-82) and that antibodies capable of blocking the activity of this enzyme can abrogate tumor growth (Drebin et al., 1988, Oncogene 2:387-394). Blocking the signal transduction capability of tyrosine phosphatases such as Flk-1 and the PDGF receptor have been shown to block tumor growth in animal models (Millauer et al., 1994, Nature 367:577; Ueno et al., Science, 252:844-848).

Relatively less is known with respect to the direct role of phosphatases in signal transduction; PPs may play a role in human diseases. For example, ectopic expression of RPTP.alpha. produces a transformed phenotype in embryonic fibroblasts (Zheng et al., Nature 359:336-339), and overexpression of RPTP.alpha. in embryonal carcinoma cells causes the cells to differentiate into a cell type with neuronal phenotype (den Hertog et al., EMBO J 12:3789-3798). The gene for human RPTP.gamma. has been localized to chromosome 3p21 which is a segment frequently altered in renal and small lung carcinoma. Mutations may occur in the extracellular segment of RPTP.gamma. which renders a RPTP that no longer respond to external signals (LaForgia et al., Wary et al., 1993, Cancer Res

52:478-482). Mutations in the gene encoding PTP1C (also known as HCP, SHP) are the cause of the moth-eaten phenotype in mice that suffer severe immunodeficiency, and systemic autoimmune disease accompanied by hyperproliferation of macrophages (Schultz et al., 1993, Cell 73:1445-1454). PTP1D (also known as Syp or PTP2C) has been shown to bind through SH2 domains to sites of phosphorylation in PDGFR, EGFR and insulin receptor substrate 1 (IRS-1). Reducing the activity of PTP1D by microinjection of anti-PTP1D antibody has been shown to block insulin or EGF-induced mitogenesis (Xiao et al., 1994, J Biol Chem 269:21244-21248).

The discovery of a new human protein phosphatase and the polynucleotides encoding it satisfies a need in the art by providing new compositions that are useful in the diagnosis, prevention and treatment of biological processes associated with abnormal or unwanted protein phosphorylation.

The phosphatase gene of the present invention can be expressed in yeast to identify possible interactors and substrates; this can be done by means of a complementation assay or a two-hybrid experiment. Artificially synthesized enzyme as well as derived peptides can be used to activate or inhibit cellular processes modulated by this phosphatase. Immunoassay or PCR may be used to measure the concentration of this protein and detect abnormally developing tissue or cancerous growth.

For a review of the phosphatase associated with the present invention see Wishart *et al., J Biol Chem* 1995 Nov 10;270(45):26782-5, Bjorge *et al., J Biol Chem* 2000 Sep 27; Harroch *et al., Mol Cell Biol* 2000 Oct;20(20):7706-15, Beghini *et al., Hum Mol Genet* 2000 Sep 22;9(15):2297-2304, Waddleton *et al., Anal Biochem* 2000 Oct 1;285(1):58-63.

SUMMARY OF THE INVENTION

The present invention is based in part on the identification of amino acid sequences of human phosphatase peptides and proteins that are related to the protein tyrosine phosphatase subfamily, as well as allelic variants and other mammalian orthologs thereof. These unique peptide sequences, and nucleic acid sequences that encode these peptides, can be used as models for the development of human therapeutic targets, aid in the identification of therapeutic proteins, and serve as targets for the development of human therapeutic agents that modulate phosphatase activity in cells and tissues that express the phosphatase. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as

well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues.

DESCRIPTION OF THE FIGURE SHEETS

FIGURE 1 provides the nucleotide sequence of a cDNA molecule or transcript sequence that encodes the phosphatase protein of the present invention. (SEQ ID NO:1) In addition, structure and functional information is provided, such as ATG start, stop and tissue distribution, where available, that allows one to readily determine specific uses of inventions based on this molecular sequence. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues.

FIGURE 2 provides the predicted amino acid sequence of the phosphatase of the present invention. (SEQ ID NO:2) In addition structure and functional information such as protein family, function, and modification sites is provided where available, allowing one to readily determine specific uses of inventions based on this molecular sequence.

FIGURE 3 provides genomic sequences that span the gene encoding the phosphatase protein of the present invention. (SEQ ID NO:3) In addition structure and functional information, such as intron/exon structure, promoter location, etc., is provided where available, allowing one to readily determine specific uses of inventions based on this molecular sequence. As illustrated in Figure 3, known SNP variations include G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G, C39269G, -20999T, -4004A, and G20988-.

DETAILED DESCRIPTION OF THE INVENTION

General Description

The present invention is based on the sequencing of the human genome. During the sequencing and assembly of the human genome, analysis of the sequence information revealed previously unidentified fragments of the human genome that encode peptides that share structural and/or sequence homology to protein/peptide/domains identified and characterized within the art as being a phosphatase protein or part of a phosphatase protein

and are related to the protein tyrosine phosphatase subfamily. Utilizing these sequences, additional genomic sequences were assembled and transcript and/or cDNA sequences were isolated and characterized. Based on this analysis, the present invention provides amino acid sequences of human phosphatase peptides and proteins that are related to the protein tyrosine phosphatase subfamily, nucleic acid sequences in the form of transcript sequences, cDNA sequences and/or genomic sequences that encode these phosphatase peptides and proteins, nucleic acid variation (allelic information), tissue distribution of expression, and information about the closest art known protein/peptide/domain that has structural or sequence homology to the phosphatase of the present invention.

In addition to being previously unknown, the peptides that are provided in the present invention are selected based on their ability to be used for the development of commercially important products and services. Specifically, the present peptides are selected based on homology and/or structural relatedness to known phosphatase proteins of the protein tyrosine phosphatase subfamily and the expression pattern observed. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. The art has clearly established the commercial importance of members of this family of proteins and proteins that have expression patterns similar to that of the present gene. Some of the more specific features of the peptides of the present invention, and the uses thereof, are described herein, particularly in the Background of the Invention and in the annotation provided in the Figures, and/or are known within the art for each of the known phosphatase family or subfamily of phosphatase proteins.

Specific Embodiments

Peptide Molecules

The present invention provides nucleic acid sequences that encode protein molecules that have been identified as being members of the phosphatase family of proteins and are related to the protein tyrosine phosphatase subfamily (protein sequences are provided in Figure 2, transcript/cDNA sequences are provided in Figure 1 and genomic sequences are provided in Figure 3). The peptide sequences provided in Figure 2, as well as the obvious variants described herein, particularly allelic variants as identified herein and using the

information in Figure 3, will be referred herein as the phosphatase peptides of the present invention, phosphatase peptides, or peptides/proteins of the present invention.

The present invention provides isolated peptide and protein molecules that consist of, consist essentially of, or comprise the amino acid sequences of the phosphatase peptides disclosed in the Figure 2, (encoded by the nucleic acid molecule shown in Figure 1, transcript/cDNA or Figure 3, genomic sequence), as well as all obvious variants of these peptides that are within the art to make and use. Some of these variants are described in detail below.

As used herein, a peptide is said to be "isolated" or "purified" when it is substantially free of cellular material or free of chemical precursors or other chemicals. The peptides of the present invention can be purified to homogeneity or other degrees of purity. The level of purification will be based on the intended use. The critical feature is that the preparation allows for the desired function of the peptide, even if in the presence of considerable amounts of other components (the features of an isolated nucleic acid molecule is discussed below).

In some uses, "substantially free of cellular material" includes preparations of the peptide having less than about 30% (by dry weight) other proteins (i.e., contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins. When the peptide is recombinantly produced, it can also be substantially free of culture medium, i.e., culture medium represents less than about 20% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of the peptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the phosphatase peptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

The isolated phosphatase peptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. For example, a nucleic acid molecule encoding the phosphatase peptide is cloned into an expression vector, the

In some uses, the fusion protein does not affect the activity of the phosphatase peptide *per se*. For example, the fusion protein can include, but is not limited to, enzymatic fusion proteins, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate the purification of recombinant phosphatase peptide. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence.

A chimeric or fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different protein sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A phosphatase peptide-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the phosphatase peptide.

As mentioned above, the present invention also provides and enables obvious variants of the amino acid sequence of the proteins of the present invention, such as naturally occurring mature forms of the peptide, allelic/sequence variants of the peptides, non-naturally occurring recombinantly derived variants of the peptides, and orthologs and paralogs of the peptides. Such variants can readily be generated using art-known techniques in the fields of recombinant nucleic acid technology and protein biochemistry. It is understood, however, that variants exclude any amino acid sequences disclosed prior to the invention.

Such variants can readily be identified/made using molecular techniques and the sequence information disclosed herein. Further, such variants can readily be distinguished from other peptides based on sequence and/or structural homology to the phosphatase peptides of the present invention. The degree of homology/identity present will be based primarily on whether the peptide is a functional variant or non-functional variant, the amount of divergence present in the paralog family and the evolutionary distance between the orthologs.

To determine the percent identity of two amino acid sequences or two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for

optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% or more of the length of a reference sequence is aligned for comparison purposes. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity and similarity between two sequences can be accomplished using a mathematical algorithm. (*Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part 1*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux, J., *et al.*, *Nucleic Acids Res. 12(1)*:387 (1984)) (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Myers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the

NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (*J. Mol. Biol.* 215:403-10 (1990)). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (*Nucleic Acids Res.* 25(17):3389-3402 (1997)). When utilizing BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

Full-length pre-processed forms, as well as mature processed forms, of proteins that comprise one of the peptides of the present invention can readily be identified as having complete sequence identity to one of the phosphatase peptides of the present invention as well as being encoded by the same genetic locus as the phosphatase peptide provided herein. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 14 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AL139317.2, which is known to be located on human chromosome 14.

Allelic variants of a phosphatase peptide can readily be identified as being a human protein having a high degree (significant) of sequence homology/identity to at least a portion of the phosphatase peptide as well as being encoded by the same genetic locus as the phosphatase peptide provided herein. Genetic locus can readily be determined based on the genomic information provided in Figure 3, such as the genomic sequence mapped to the reference human. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 14 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AL139317.2, which is known to be located on human chromosome 14. As used herein, two proteins (or a region of the proteins) have significant homology when the amino acid sequences are typically at least about 70-80%, 80-90%, and more typically at least about 90-95% or more homologous. A significantly homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid sequence that will hybridize to a phosphatase peptide encoding nucleic acid molecule under stringent conditions as more fully described below.

Figure 3 provides SNP information that has been found in a gene encoding the phosphatase protein of the present invention. The following variations were seen: G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G and C39269G as substitutions, -20999T, -4004A as insertions and G20988- deletion. The changes in the amino acid sequence that these SNPs cause can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a base.

Paralogs of a phosphatase peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the phosphatase peptide, as being encoded by a gene from humans, and as having similar activity or function. Two proteins will typically be considered paralogs when the amino acid sequences are typically at least about 60% or greater, and more typically at least about 70% or greater homology through a given region or domain. Such paralogs will be encoded by a nucleic acid sequence that will hybridize to a phosphatase peptide encoding nucleic acid molecule under moderate to stringent conditions as more fully described below.

Orthologs of a phosphatase peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the phosphatase peptide as well as being encoded by a gene from another organism. Preferred orthologs will be isolated from mammals, preferably primates, for the development of human therapeutic targets and agents. Such orthologs will be encoded by a nucleic acid sequence that will hybridize to a phosphatase peptide encoding nucleic acid molecule under moderate to stringent conditions, as more fully described below, depending on the degree of relatedness of the two organisms yielding the proteins.

Non-naturally occurring variants of the phosphatase peptides of the present invention can readily be generated using recombinant techniques. Such variants include, but are not limited to deletions, additions and substitutions in the amino acid sequence of the phosphatase peptide. For example, one class of substitutions are conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a phosphatase peptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which

amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science* *247*:1306-1310 (1990).

Variant phosphatase peptides can be fully functional or can lack function in one or more activities, e.g. ability to bind substrate, ability to dephosphorylate substrate, ability to mediate signaling, etc. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Figure 2 provides the result of protein analysis and can be used to identify critical domains/regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree.

Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science 244*:1081-1085 (1989)), particularly using the results provided in Figure 2. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as phosphatase activity or in assays such as an *in vitro* proliferative activity. Sites that are critical for binding partner/substrate binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al., J. Mol. Biol. 224*:899-904 (1992); de Vos *et al.* *Science 255*:306-312 (1992)).

The present invention further provides fragments of the phosphatase peptides, in addition to proteins and peptides that comprise and consist of such fragments, particularly those comprising the residues identified in Figure 2. The fragments to which the invention pertains, however, are not to be construed as encompassing fragments that may be disclosed publicly prior to the present invention.

As used herein, a fragment comprises at least 8, 10, 12, 14, 16, or more contiguous amino acid residues from a phosphatase peptide. Such fragments can be chosen based on the ability to retain one or more of the biological activities of the phosphatase peptide or could be chosen for the ability to perform a function, e.g. bind a substrate or act as an immunogen. Particularly important fragments are biologically active fragments, peptides that are, for example, about 8 or more amino acids in length. Such fragments will typically comprise a domain or motif of the phosphatase peptide, e.g., active site, a transmembrane domain or a

substrate-binding domain. Further, possible fragments include, but are not limited to, domain or motif containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well known and readily available to those of skill in the art (e.g., PROSITE analysis). The results of one such analysis are provided in Figure 2.

Polypeptides often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Common modifications that occur naturally in phosphatase peptides are described in basic texts, detailed monographs, and the research literature, and they are well known to those of skill in the art (some of these features are identified in Figure 2).

Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

Such modifications are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins - Structure and Molecular Properties*, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as by Wold, F., *Posttranslational Covalent Modification of Proteins*, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter *et al.* (*Meth. Enzymol. 182*: 626-646 (1990)) and Rattan *et al.* (*Ann. N.Y. Acad. Sci. 663*:48-62 (1992)).

Accordingly, the phosphatase peptides of the present invention also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature phosphatase peptide is fused with another compound, such as a compound to increase the half-life of the phosphatase

peptide, or in which the additional amino acids are fused to the mature phosphatase peptide, such as a leader or secretory sequence or a sequence for purification of the mature phosphatase peptide or a pro-protein sequence.

Protein/Peptide Uses

The proteins of the present invention can be used in substantial and specific assays related to the functional information provided in the Figures; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its binding partner or ligand) in biological fluids; and as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state). Where the protein binds or potentially binds to another protein or ligand (such as, for example, in a phosphatase-effector protein interaction or phosphatase-ligand interaction), the protein can be used to identify the binding partner/ligand so as to develop a system to identify inhibitors of the binding interaction. Any or all of these uses are capable of being developed into reagent grade or kit format for commercialization as commercial products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

The potential uses of the peptides of the present invention are based primarily on the source of the protein as well as the class/action of the protein. For example, phosphatases isolated from humans and their human/mammalian orthologs serve as targets for identifying agents for use in mammalian therapeutic applications, e.g. a human drug, particularly in modulating a biological or pathological response in a cell or tissue that expresses the phosphatase. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid. A large percentage of

pharmaceutical agents are being developed that modulate the activity of phosphatase proteins, particularly members of the protein tyrosine phosphatse subfamily (see Background of the Invention). The structural and functional information provided in the Background and Figures provide specific and substantial uses for the molecules of the present invention, particularly in combination with the expression information provided in Figure 1. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. Such uses can readily be determined using the information provided herein, that which is known in the art, and routine experimentation.

The proteins of the present invention (including variants and fragments that may have been disclosed prior to the present invention) are useful for biological assays related to phosphatases that are related to members of the protein tyrosine phosphatse subfamily. Such assays involve any of the known phosphatase functions or activities or properties useful for diagnosis and treatment of phosphatase-related conditions that are specific for the subfamily of protein tyrosine phosphatases that the one of the present invention belongs to, particularly in cells and tissues that express the phosphatase. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid.

The proteins of the present invention are also useful in drug screening assays, in cell-based or cell-free systems. Cell-based systems can be native, i.e., cells that normally express the phosphatase, as a biopsy or expanded in cell culture. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. In an alternate embodiment, cell-based assays involve recombinant host cells expressing the phosphatase protein.

The polypeptides can be used to identify compounds that modulate phosphatase activity of the protein in its natural state or an altered form that causes a specific disease or pathology associated with the phosphatase. Both the phosphatases of the present invention and appropriate variants and fragments can be used in high-throughput screens to assay candidate compounds

for the ability to bind to the phosphatase. These compounds can be further screened against a functional phosphatase to determine the effect of the compound on the phosphatase activity. Further, these compounds can be tested in animal or invertebrate systems to determine activity/effectiveness. Compounds can be identified that activate (agonist) or inactivate (antagonist) the phosphatase to a desired degree.

Further, the proteins of the present invention can be used to screen a compound for the ability to stimulate or inhibit interaction between the phosphatase protein and a molecule that normally interacts with the phosphatase protein, e.g. a substrate or a component of the signal pathway that the phosphatase protein normally interacts (for example, another phosphatase). Such assays typically include the steps of combining the phosphatase protein with a candidate compound under conditions that allow the phosphatase protein, or fragment, to interact with the target molecule, and to detect the formation of a complex between the protein and the target or to detect the biochemical consequence of the interaction with the phosphatase protein and the target, such as any of the associated effects of signal transduction such as protein phosphorylation, cAMP turnover, and adenylate cyclase activation, etc.

Candidate compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam *et al.*, *Nature 354*:82-84 (1991); Houghten *et al.*, *Nature 354*:84-86 (1991)) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang *et al.*, *Cell 72*:767-778 (1993)); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, $F(ab')_2$, Fab expression library fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules (e.g., molecules obtained from combinatorial and natural product libraries).

One candidate compound is a soluble fragment of the receptor that competes for substrate binding. Other candidate compounds include mutant phosphatases or appropriate fragments containing mutations that affect phosphatase function and thus compete for substrate. Accordingly, a fragment that competes for substrate, for example with a higher affinity, or a fragment that binds substrate but does not allow release, is encompassed by the invention.

The invention further includes other end point assays to identify compounds that modulate (stimulate or inhibit) phosphatase activity. The assays typically involve an assay of events in the signal transduction pathway that indicate phosphatase activity. Thus, the dephosphorylation of a substrate, activation of a protein, a change in the expression of genes that

are up- or down-regulated in response to the phosphatase protein dependent signal cascade can be assayed.

Any of the biological or biochemical functions mediated by the phosphatase can be used as an endpoint assay. These include all of the biochemical or biochemical/biological events described herein, in the references cited herein, incorporated by reference for these endpoint assay targets, and other functions known to those of ordinary skill in the art or that can be readily identified using the information provided in the Figures, particularly Figure 2. Specifically, a biological function of a cell or tissues that expresses the phosphatase can be assayed. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid.

Binding and/or activating compounds can also be screened by using chimeric phosphatase proteins in which the amino terminal extracellular domain, or parts thereof, the entire transmembrane domain or subregions, such as any of the seven transmembrane segments or any of the intracellular or extracellular loops and the carboxy terminal intracellular domain, or parts thereof, can be replaced by heterologous domains or subregions. For example, a substrate-binding region can be used that interacts with a different substrate then that which is recognized by the native phosphatase. Accordingly, a different set of signal transduction components is available as an end-point assay for activation. This allows for assays to be performed in other than the specific host cell from which the phosphatase is derived.

The proteins of the present invention are also useful in competition binding assays in methods designed to discover compounds that interact with the phosphatase (e.g. binding partners and/or ligands). Thus, a compound is exposed to a phosphatase polypeptide under conditions that allow the compound to bind or to otherwise interact with the polypeptide. Soluble phosphatase polypeptide is also added to the mixture. If the test compound interacts with the soluble phosphatase polypeptide, it decreases the amount of complex formed or activity from the phosphatase target. This type of assay is particularly useful in cases in which compounds are sought that interact with specific regions of the phosphatase. Thus, the soluble polypeptide that competes with the target phosphatase region is designed to contain peptide sequences corresponding to the region of interest.

To perform cell free drug screening assays, it is sometimes desirable to immobilize either the phosphatase protein, or fragment, or its target molecule to facilitate separation of complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay.

Techniques for immobilizing proteins on matrices can be used in the drug screening assays. In one embodiment, a fusion protein can be provided which adds a domain that allows the protein to be bound to a matrix. For example, glutathione-S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the cell lysates (e.g., ^{35}S-labeled) and the candidate compound, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads are washed to remove any unbound label, and the matrix immobilized and radiolabel determined directly, or in the supernatant after the complexes are dissociated. Alternatively, the complexes can be dissociated from the matrix, separated by SDS-PAGE, and the level of phosphatase-binding protein found in the bead fraction quantitated from the gel using standard electrophoretic techniques. For example, either the polypeptide or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin using techniques well known in the art. Alternatively, antibodies reactive with the protein but which do not interfere with binding of the protein to its target molecule can be derivatized to the wells of the plate, and the protein trapped in the wells by antibody conjugation. Preparations of a phosphatase-binding protein and a candidate compound are incubated in the phosphatase protein-presenting wells and the amount of complex trapped in the well can be quantitated. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the phosphatase protein target molecule, or which are reactive with phosphatase protein and compete with the target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the target molecule.

Agents that modulate one of the phosphatases of the present invention can be identified using one or more of the above assays, alone or in combination. It is generally preferable to use a cell-based or cell free system first and then confirm activity in an animal or other model system. Such model systems are well known in the art and can readily be employed in this context.

Modulators of phosphatase protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the kinase pathway, by treating

cells or tissues that express the phosphatase. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. These methods of treatment include the steps of administering a modulator of phosphatase activity in a pharmaceutical composition to a subject in need of such treatment, the modulator being identified as described herein.

In yet another aspect of the invention, the phosphatase proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with the phosphatase and are involved in phosphatase activity. Such phosphatase-binding proteins are also likely to be involved in the propagation of signals by the phosphatase proteins or phosphatase targets as, for example, downstream elements of a kinase-mediated signaling pathway. Alternatively, such phosphatase-binding proteins are likely to be phosphatase inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a phosphatase protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo,* forming a phosphatase-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the phosphatase protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent

identified as described herein (e.g., a phosphatase-modulating agent, an antisense phosphatase nucleic acid molecule, a phosphatase-specific antibody, or a phosphatase-binding partner) can be used in an animal or other model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal or other model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

The phosphatase proteins of the present invention are also useful to provide a target for diagnosing a disease or predisposition to disease mediated by the peptide. Accordingly, the invention provides methods for detecting the presence, or levels of, the protein (or encoding mRNA) in a cell, tissue, or organism. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. The method involves contacting a biological sample with a compound capable of interacting with the phosphatase protein such that the interaction can be detected. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

One agent for detecting a protein in a sample is an antibody capable of selectively binding to protein. A biological sample includes tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The peptides of the present invention also provide targets for diagnosing active protein activity, disease, or predisposition to disease, in a patient having a variant peptide, particularly activities and conditions that are known for other members of the family of proteins to which the present one belongs. Thus, the peptide can be isolated from a biological sample and assayed for the presence of a genetic mutation that results in aberrant peptide. This includes amino acid substitution, deletion, insertion, rearrangement, (as the result of aberrant splicing events), and inappropriate post-translational modification. Analytic methods include altered electrophoretic mobility, altered tryptic peptide digest, altered phosphatase activity in cell-based or cell-free assay, alteration in substrate or antibody-binding pattern, altered isoelectric point, direct amino acid sequencing, and any other of the known assay techniques useful for detecting mutations in a protein. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

In vitro techniques for detection of peptide include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence using a

detection reagent, such as an antibody or protein binding agent. Alternatively, the peptide can be detected *in vivo* in a subject by introducing into the subject a labeled anti-peptide antibody or other types of detection agent. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. Particularly useful are methods that detect the allelic variant of a peptide expressed in a subject and methods which detect fragments of a peptide in a sample.

The peptides are also useful in pharmacogenomic analysis. Pharmacogenomics deal with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Eichelbaum, M. (*Clin. Exp. Pharmacol. Physiol.* 23(10-11):983-985 (1996)), and Linder, M.W. (*Clin. Chem.* 43(2):254-266 (1997)). The clinical outcomes of these variations result in severe toxicity of therapeutic drugs in certain individuals or therapeutic failure of drugs in certain individuals as a result of individual variation in metabolism. Thus, the genotype of the individual can determine the way a therapeutic compound acts on the body or the way the body metabolizes the compound. Further, the activity of drug metabolizing enzymes effects both the intensity and duration of drug action. Thus, the pharmacogenomics of the individual permit the selection of effective compounds and effective dosages of such compounds for prophylactic or therapeutic treatment based on the individual's genotype. The discovery of genetic polymorphisms in some drug metabolizing enzymes has explained why some patients do not obtain the expected drug effects, show an exaggerated drug effect, or experience serious toxicity from standard drug dosages. Polymorphisms can be expressed in the phenotype of the extensive metabolizer and the phenotype of the poor metabolizer. Accordingly, genetic polymorphism may lead to allelic protein variants of the phosphatase protein in which one or more of the phosphatase functions in one population is different from those in another population. The peptides thus allow a target to ascertain a genetic predisposition that can affect treatment modality. Thus, in a ligand-based treatment, polymorphism may give rise to amino terminal extracellular domains and/or other substrate-binding regions that are more or less active in substrate binding, and phosphatase activation. Accordingly, substrate dosage would necessarily be modified to maximize the therapeutic effect within a given population containing a polymorphism. As an alternative to genotyping, specific polymorphic peptides could be identified.

The peptides are also useful for treating a disorder characterized by an absence of, inappropriate, or unwanted expression of the protein. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human

brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. Accordingly, methods for treatment include the use of the phosphatase protein or fragments.

Antibodies

The invention also provides antibodies that selectively bind to one of the peptides of the present invention, a protein comprising such a peptide, as well as variants and fragments thereof. As used herein, an antibody selectively binds a target peptide when it binds the target peptide and does not significantly bind to unrelated proteins. An antibody is still considered to selectively bind a peptide even if it also binds to other proteins that are not substantially homologous with the target peptide so long as such proteins share homology with a fragment or domain of the peptide target of the antibody. In this case, it would be understood that antibody binding to the peptide is still selective despite some degree of cross-reactivity.

As used herein, an antibody is defined in terms consistent with that recognized within the art: they are multi-subunit proteins produced by a mammalian organism in response to an antigen challenge. The antibodies of the present invention include polyclonal antibodies and monoclonal antibodies, as well as fragments of such antibodies, including, but not limited to, Fab or $F(ab')_2$, and Fv fragments.

Many methods are known for generating and/or identifying antibodies to a given target peptide. Several such methods are described by Harlow, Antibodies, Cold Spring Harbor Press, (1989).

In general, to generate antibodies, an isolated peptide is used as an immunogen and is administered to a mammalian organism, such as a rat, rabbit or mouse. The full-length protein, an antigenic peptide fragment or a fusion protein can be used. Particularly important fragments are those covering functional domains, such as the domains identified in Figure 2, and domain of sequence homology or divergence amongst the family, such as those that can readily be identified using protein alignment methods and as presented in the Figures.

Antibodies are preferably prepared from regions or discrete fragments of the phosphatase proteins. Antibodies can be prepared from any region of the peptide as described herein. However, preferred regions will include those involved in function/activity and/or phosphatase/binding partner interaction. Figure 2 can be used to identify particularly important regions while sequence alignment can be used to identify conserved and unique sequence fragments.

An antigenic fragment will typically comprise at least 8 contiguous amino acid residues. The antigenic peptide can comprise, however, at least 10, 12, 14, 16 or more amino acid residues. Such fragments can be selected on a physical property, such as fragments correspond to regions that are located on the surface of the protein, e.g., hydrophilic regions or can be selected based on sequence uniqueness (see Figure 2).

Detection on an antibody of the present invention can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibody Uses

The antibodies can be used to isolate one of the proteins of the present invention by standard techniques, such as affinity chromatography or immunoprecipitation. The antibodies can facilitate the purification of the natural protein from cells and recombinantly produced protein expressed in host cells. In addition, such antibodies are useful to detect the presence of one of the proteins of the present invention in cells or tissues to determine the pattern of expression of the protein among various tissues in an organism and over the course of normal development. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid. Further, such antibodies can be used to detect protein *in situ*, *in vitro*, or in a cell lysate or supernatant in order to evaluate the abundance and pattern of expression. Also, such antibodies can be used to assess abnormal tissue distribution or abnormal

expression during development or progression of a biological condition. Antibody detection of circulating fragments of the full length protein can be used to identify turnover.

Further, the antibodies can be used to assess expression in disease states such as in active stages of the disease or in an individual with a predisposition toward disease related to the protein's function. When a disorder is caused by an inappropriate tissue distribution, developmental expression, level of expression of the protein, or expressed/processed form, the antibody can be prepared against the normal protein. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. If a disorder is characterized by a specific mutation in the protein, antibodies specific for this mutant protein can be used to assay for the presence of the specific mutant protein.

The antibodies can also be used to assess normal and aberrant subcellular localization of cells in the various tissues in an organism. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting expression level or the presence of aberrant sequence and aberrant tissue distribution or developmental expression, antibodies directed against the protein or relevant fragments can be used to monitor therapeutic efficacy.

Additionally, antibodies are useful in pharmacogenomic analysis. Thus, antibodies prepared against polymorphic proteins can be used to identify individuals that require modified treatment modalities. The antibodies are also useful as diagnostic tools as an immunological marker for aberrant protein analyzed by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays known to those in the art.

The antibodies are also useful for tissue typing. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. Thus, where a specific protein has been correlated with expression in a specific tissue, antibodies that are specific for this protein can be used to identify a tissue type.

The antibodies are also useful for inhibiting protein function, for example, blocking the binding of the phosphatase peptide to a binding partner such as a substrate. These uses can also

be applied in a therapeutic context in which treatment involves inhibiting the protein's function. An antibody can be used, for example, to block binding, thus modulating (agonizing or antagonizing) the peptides activity. Antibodies can be prepared against specific fragments containing sites required for function or against intact protein that is associated with a cell or cell membrane. See Figure 2 for structural information relating to the proteins of the present invention.

The invention also encompasses kits for using antibodies to detect the presence of a protein in a biological sample. The kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting protein in a biological sample; means for determining the amount of protein in the sample; means for comparing the amount of protein in the sample with a standard; and instructions for use. Such a kit can be supplied to detect a single protein or epitope or can be configured to detect one of a multitude of epitopes, such as in an antibody detection array. Arrays are described in detail below for nuleic acid arrays and similar methods have been developed for antibody arrays.

Nucleic Acid Molecules

The present invention further provides isolated nucleic acid molecules that encode a phosphatase peptide or protein of the present invention (cDNA, transcript and genomic sequence). Such nucleic acid molecules will consist of, consist essentially of, or comprise a nucleotide sequence that encodes one of the phosphatase peptides of the present invention, an allelic variant thereof, or an ortholog or paralog thereof.

As used herein, an "isolated" nucleic acid molecule is one that is separated from other nucleic acid present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. However, there can be some flanking nucleotide sequences, for example up to about 5KB, 4KB, 3KB, 2KB, or 1KB or less, particularly contiguous peptide encoding sequences and peptide encoding sequences within the same gene but separated by introns in the genomic sequence. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences such that it can be subjected to the specific manipulations described herein such as recombinant expression, preparation of probes and primers, and other uses specific to the nucleic acid sequences.

Moreover, an "isolated" nucleic acid molecule, such as a transcript/cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by

recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated.

For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the isolated DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Accordingly, the present invention provides nucleic acid molecules that consist of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule consists of a nucleotide sequence when the nucleotide sequence is the complete nucleotide sequence of the nucleic acid molecule.

The present invention further provides nucleic acid molecules that consist essentially of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule consists essentially of a nucleotide sequence when such a nucleotide sequence is present with only a few additional nucleic acid residues in the final nucleic acid molecule.

The present invention further provides nucleic acid molecules that comprise the nucleotide sequences shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule comprises a nucleotide sequence when the nucleotide sequence is at least part of the final nucleotide sequence of the nucleic acid molecule. In such a fashion, the nucleic acid molecule can be only the nucleotide sequence or have additional nucleic acid residues, such as nucleic acid residues that are naturally associated with it or heterologous nucleotide sequences. Such a nucleic acid molecule can have a few additional nucleotides or can comprises several hundred or more additional nucleotides. A brief description of how various types of these nucleic acid molecules can be readily made/isolated is provided below.

In Figures 1 and 3, both coding and non-coding sequences are provided. Because of the source of the present invention, humans genomic sequence (Figure 3) and cDNA/transcript sequences (Figure 1), the nucleic acid molecules in the Figures will contain

genomic intronic sequences, 5' and 3' non-coding sequences, gene regulatory regions and non-coding intergenic sequences. In general such sequence features are either noted in Figures 1 and 3 or can readily be identified using computational tools known in the art. As discussed below, some of the non-coding regions, particularly gene regulatory elements such as promoters, are useful for a variety of purposes, e.g. control of heterologous gene expression, target for identifying gene activity modulating compounds, and are particularly claimed as fragments of the genomic sequence provided herein.

The isolated nucleic acid molecules can encode the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature peptide (when the mature form has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life or facilitate manipulation of a protein for assay or production, among other things. As generally is the case *in situ*, the additional amino acids may be processed away from the mature protein by cellular enzymes.

As mentioned above, the isolated nucleic acid molecules include, but are not limited to, the sequence encoding the phosphatase peptide alone, the sequence encoding the mature peptide and additional coding sequences, such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), the sequence encoding the mature peptide, with or without the additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but non-translated sequences that play a role in transcription, mRNA processing (including splicing and polyadenylation signals), ribosome binding and stability of mRNA. In addition, the nucleic acid molecule may be fused to a marker sequence encoding, for example, a peptide that facilitates purification.

Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

The invention further provides nucleic acid molecules that encode fragments of the peptides of the present invention as well as nucleic acid molecules that encode obvious variants of the phosphatase proteins of the present invention that are described above. Such nucleic acid molecules may be naturally occurring, such as allelic variants (same locus), paralogs (different locus), and orthologs (different organism), or may be constructed by recombinant DNA methods or by chemical synthesis. Such non-naturally occurring variants may be made by mutagenesis

techniques, including those applied to nucleic acid molecules, cells, or organisms. Accordingly, as discussed above, the variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions.

The present invention further provides non-coding fragments of the nucleic acid molecules provided in Figures 1 and 3. Preferred non-coding fragments include, but are not limited to, promoter sequences, enhancer sequences, gene modulating sequences and gene termination sequences. Such fragments are useful in controlling heterologous gene expression and in developing screens to identify gene-modulating agents. A promoter can readily be identified as being 5' to the ATG start site in the genomic sequence provided in Figure 3.

A fragment comprises a contiguous nucleotide sequence greater than 12 or more nucleotides. Further, a fragment could at least 30, 40, 50, 100, 250 or 500 nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope bearing regions of the peptide, or can be useful as DNA probes and primers. Such fragments can be isolated using the known nucleotide sequence to synthesize an oligonucleotide probe. A labeled probe can then be used to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in PCR reactions to clone specific regions of gene.

A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides.

Orthologs, homologs, and allelic variants can be identified using methods well known in the art. As described in the Peptide Section, these variants comprise a nucleotide sequence encoding a peptide that is typically 60-70%, 70-80%, 80-90%, and more typically at least about 90-95% or more homologous to the nucleotide sequence shown in the Figure sheets or a fragment of this sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under moderate to stringent conditions, to the nucleotide sequence shown in the Figure sheets or a fragment of the sequence. Allelic variants can readily be determined by genetic locus of the encoding gene. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 14 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AL139317.2, which is known to be located on human chromosome 14.

Figure 3 provides SNP information that has been found in a gene encoding the phosphatase protein of the present invention. The following variations were seen: G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G and C39269G as substitutions, -20999T, -4004A as insertions and G20988- deletion. The changes in the amino acid sequence that these SNPs cause can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a base.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 60-70% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 60%, at least about 70%, or at least about 80% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65C. Examples of moderate to low stringency hybridization conditions are well known in the art.

Nucleic Acid Molecule Uses

The nucleic acid molecules of the present invention are useful for probes, primers, chemical intermediates, and in biological assays. The nucleic acid molecules are useful as a hybridization probe for messenger RNA, transcript/cDNA and genomic DNA to isolate full-length cDNA and genomic clones encoding the peptide described in Figure 2 and to isolate cDNA and genomic clones that correspond to variants (alleles, orthologs, etc.) producing the same or related peptides shown in Figure 2. As illustrated in Figure 3, known SNP variations include G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G, C39269G, -20999T, -4004A, and G20988-.

The probe can correspond to any sequence along the entire length of the nucleic acid molecules provided in the Figures. Accordingly, it could be derived from 5' noncoding regions, the coding region, and 3' noncoding regions. However, as discussed, fragments are not to be construed as encompassing fragments disclosed prior to the present invention.

The nucleic acid molecules are also useful as primers for PCR to amplify any given region of a nucleic acid molecule and are useful to synthesize antisense molecules of desired length and sequence.

The nucleic acid molecules are also useful for constructing recombinant vectors. Such vectors include expression vectors that express a portion of, or all of, the peptide sequences. Vectors also include insertion vectors, used to integrate into another nucleic acid molecule sequence, such as into the cellular genome, to alter *in situ* expression of a gene and/or gene product. For example, an endogenous coding sequence can be replaced via homologous recombination with all or part of the coding region containing one or more specifically introduced mutations.

The nucleic acid molecules are also useful for expressing antigenic portions of the proteins.

The nucleic acid molecules are also useful as probes for determining the chromosomal positions of the nucleic acid molecules by means of *in situ* hybridization methods. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 14 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AL139317.2, which is known to be located on human chromosome 14.

The nucleic acid molecules are also useful in making vectors containing the gene regulatory regions of the nucleic acid molecules of the present invention.

The nucleic acid molecules are also useful for designing ribozymes corresponding to all, or a part, of the mRNA produced from the nucleic acid molecules described herein.

The nucleic acid molecules are also useful for making vectors that express part, or all, of the peptides.

The nucleic acid molecules are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful as hybridization probes for determining the presence, level, form and distribution of nucleic acid expression. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain,

human brain, human heart, human liver, human lung, human placenta, and human thyroid. Accordingly, the probes can be used to detect the presence of, or to determine levels of, a specific nucleic acid molecule in cells, tissues, and in organisms. The nucleic acid whose level is determined can be DNA or RNA. Accordingly, probes corresponding to the peptides described herein can be used to assess expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in phosphatase protein expression relative to normal results.

In vitro techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detecting DNA includes Southern hybridizations and *in situ* hybridization.

Probes can be used as a part of a diagnostic test kit for identifying cells or tissues that express a phosphatase protein, such as by measuring a level of a phosphatase-encoding nucleic acid in a sample of cells from a subject e.g., mRNA or genomic DNA, or determining if a phosphatase gene has been mutated. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid.

Nucleic acid expression assays are useful for drug screening to identify compounds that modulate phosphatase nucleic acid expression.

The invention thus provides a method for identifying a compound that can be used to treat a disorder associated with nucleic acid expression of the phosphatase gene, particularly biological and pathological processes that are mediated by the phosphatase in cells and tissues that express it. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues. The method typically includes assaying the ability of the compound to modulate the expression of the phosphatase nucleic acid and thus identifying a compound that can be used to treat a disorder characterized by undesired phosphatase nucleic acid expression. The assays can be performed in cell-based and cell-free systems. Cell-based assays include cells naturally expressing the phosphatase nucleic acid or recombinant cells genetically engineered to express specific nucleic acid sequences.

The assay for phosphatase nucleic acid expression can involve direct assay of nucleic acid levels, such as mRNA levels, or on collateral compounds involved in the signal pathway. Further, the expression of genes that are up- or down-regulated in response to the phosphatase protein signal pathway can also be assayed. In this embodiment the regulatory regions of these genes can be operably linked to a reporter gene such as luciferase.

Thus, modulators of phosphatase gene expression can be identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA determined. The level of expression of phosphatase mRNA in the presence of the candidate compound is compared to the level of expression of phosphatase mRNA in the absence of the candidate compound. The candidate compound can then be identified as a modulator of nucleic acid expression based on this comparison and be used, for example to treat a disorder characterized by aberrant nucleic acid expression. When expression of mRNA is statistically significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of nucleic acid expression. When nucleic acid expression is statistically significantly less in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of nucleic acid expression.

The invention further provides methods of treatment, with the nucleic acid as a target, using a compound identified through drug screening as a gene modulator to modulate phosphatase nucleic acid expression in cells and tissues that express the phosphatase. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid. Modulation includes both up-regulation (i.e. activation or agonization) or down-regulation (suppression or antagonization) or nucleic acid expression.

Alternatively, a modulator for phosphatase nucleic acid expression can be a small molecule or drug identified using the screening assays described herein as long as the drug or small molecule inhibits the phosphatase nucleic acid expression in the cells and tissues that express the protein. Experimental data as provided in Figure 1 indicates expression in the human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node, as well as expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid tissues.

The nucleic acid molecules are also useful for monitoring the effectiveness of modulating compounds on the expression or activity of the phosphatase gene in clinical trials or in a treatment regimen. Thus, the gene expression pattern can serve as a barometer for the continuing effectiveness of treatment with the compound, particularly with compounds to which a patient can develop resistance. The gene expression pattern can also serve as a marker indicative of a physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

The nucleic acid molecules are also useful in diagnostic assays for qualitative changes in phosphatase nucleic acid expression, and particularly in qualitative changes that lead to pathology. The nucleic acid molecules can be used to detect mutations in phosphatase genes and gene expression products such as mRNA. The nucleic acid molecules can be used as hybridization probes to detect naturally occurring genetic mutations in the phosphatase gene and thereby to determine whether a subject with the mutation is at risk for a disorder caused by the mutation. Mutations include deletion, addition, or substitution of one or more nucleotides in the gene, chromosomal rearrangement, such as inversion or transposition, modification of genomic DNA, such as aberrant methylation patterns or changes in gene copy number, such as amplification. Detection of a mutated form of the phosphatase gene associated with a dysfunction provides a diagnostic tool for an active disease or susceptibility to disease when the disease results from overexpression, underexpression, or altered expression of a phosphatase protein.

Individuals carrying mutations in the phosphatase gene can be detected at the nucleic acid level by a variety of techniques. Figure 3 provides SNP information that has been found in a gene encoding the phosphatase protein of the present invention. The following variations were seen: G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G and C39269G as substitutions, -20999T, -4004A as insertions and G20988- deletion. The changes in the amino acid sequence that these SNPs cause can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a base. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 14 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention

encoding a novel phosphatase maps to public BAC AC AL139317.2, which is known to be located on human chromosome 14. Genomic DNA can be analyzed directly or can be amplified by using PCR prior to analysis. RNA or cDNA can be used in the same way. In some uses, detection of the mutation involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.*, *Science 241*:1077-1080 (1988); and Nakazawa *et al.*, *PNAS 91*:360-364 (1994)), the latter of which can be particularly useful for detecting point mutations in the gene (see Abravaya *et al.*, *Nucleic Acids Res. 23*:675-682 (1995)). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. Deletions and insertions can be detected by a change in size of the amplified product compared to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to normal RNA or antisense DNA sequences.

Alternatively, mutations in a phosphatase gene can be directly identified, for example, by alterations in restriction enzyme digestion patterns determined by gel electrophoresis.

Further, sequence-specific ribozymes (U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site. Perfectly matched sequences can be distinguished from mismatched sequences by nuclease cleavage digestion assays or by differences in melting temperature.

Sequence changes at specific locations can also be assessed by nuclease protection assays such as RNase and S1 protection or the chemical cleavage method. Furthermore, sequence differences between a mutant phosphatase gene and a wild-type gene can be determined by direct DNA sequencing. A variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C.W., (1995) *Biotechniques 19*:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.*, *Adv. Chromatogr. 36*:127-162 (1996); and Griffin *et al.*, *Appl. Biochem. Biotechnol. 38*:147-159 (1993)).

Other methods for detecting mutations in the gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes (Myers *et al.*, *Science 230*:1242 (1985)); Cotton *et al.*, *PNAS 85*:4397 (1988); Saleeba *et al.*,

Meth. Enzymol. 217:286-295 (1992)), electrophoretic mobility of mutant and wild type nucleic acid is compared (Orita *et al.*, *PNAS 86*:2766 (1989); Cotton *et al.*, *Mutat. Res. 285*:125-144 (1993); and Hayashi *et al.*, *Genet. Anal. Tech. Appl. 9*:73-79 (1992)), and movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (Myers *et al.*, *Nature 313*:495 (1985)). Examples of other techniques for detecting point mutations include selective oligonucleotide hybridization, selective amplification, and selective primer extension.

The nucleic acid molecules are also useful for testing an individual for a genotype that while not necessarily causing the disease, nevertheless affects the treatment modality. Thus, the nucleic acid molecules can be used to study the relationship between an individual's genotype and the individual's response to a compound used for treatment (pharmacogenomic relationship). Accordingly, the nucleic acid molecules described herein can be used to assess the mutation content of the phosphatase gene in an individual in order to select an appropriate compound or dosage regimen for treatment. Figure 3 provides SNP information that has been found in a gene encoding the phosphatase protein of the present invention. The following variations were seen: G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G and C39269G as substitutions, -20999T, -4004A as insertions and G20988- deletion. The changes in the amino acid sequence that these SNPs cause can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a base.

Thus nucleic acid molecules displaying genetic variations that affect treatment provide a diagnostic target that can be used to tailor treatment in an individual. Accordingly, the production of recombinant cells and animals containing these polymorphisms allow effective clinical design of treatment compounds and dosage regimens.

The nucleic acid molecules are thus useful as antisense constructs to control phosphatase gene expression in cells, tissues, and organisms. A DNA antisense nucleic acid molecule is designed to be complementary to a region of the gene involved in transcription, preventing transcription and hence production of phosphatase protein. An antisense RNA or DNA nucleic acid molecule would hybridize to the mRNA and thus block translation of mRNA into phosphatase protein.

Alternatively, a class of antisense molecules can be used to inactivate mRNA in order to decrease expression of phosphatase nucleic acid. Accordingly, these molecules can treat a disorder characterized by abnormal or undesired phosphatase nucleic acid expression. This

technique involves cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Possible regions include coding regions and particularly coding regions corresponding to the catalytic and other functional activities of the phosphatase protein, such as substrate binding.

The nucleic acid molecules also provide vectors for gene therapy in patients containing cells that are aberrant in phosphatase gene expression. Thus, recombinant cells, which include the patient's cells that have been engineered *ex vivo* and returned to the patient, are introduced into an individual where the cells produce the desired phosphatase protein to treat the individual.

The invention also encompasses kits for detecting the presence of a phosphatase nucleic acid in a biological sample. Experimental data as provided in Figure 1 indicates that phosphatase proteins of the present invention are expressed in the human brain, heart and liver etc. Specifically, a virtual northern blot shows expression in human total fetus, human germinal B cell, human fetal liver, human fetal liver spleen and human lymph node. In addition, PCR-based tissue screening panel indicates expression in human fetal brain, human brain, human heart, human liver, human lung, human placenta, and human thyroid. For example, the kit can comprise reagents such as a labeled or labelable nucleic acid or agent capable of detecting phosphatase nucleic acid in a biological sample; means for determining the amount of phosphatase nucleic acid in the sample; and means for comparing the amount of phosphatase nucleic acid in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect phosphatase protein mRNA or DNA.

Nucleic Acid Arrays

The present invention further provides nucleic acid detection kits, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information provided in Figures 1 and 3 (SEQ ID NOS:1 and 3).

As used herein "Arrays" or "Microarrays" refers to an array of distinct polynucleotides or oligonucleotides synthesized on a substrate, such as paper, nylon or other type of membrane, filter, chip, glass slide, or any other suitable solid support. In one embodiment, the microarray is prepared and used according to the methods described in US Patent 5,837,832, Chee *et al.*, PCT application W095/11995 (Chee *et al.*), Lockhart, D. J. *et al.* (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. *et al.* (1996; Proc. Natl. Acad. Sci.

93: 10614-10619), all of which are incorporated herein in their entirety by reference. In other embodiments, such arrays are produced by the methods described by Brown *et al.*, US Patent No. 5,807,522.

The microarray or detection kit is preferably composed of a large number of unique, single-stranded nucleic acid sequences, usually either synthetic antisense oligonucleotides or fragments of cDNAs, fixed to a solid support. The oligonucleotides are preferably about 6-60 nucleotides in length, more preferably 15-30 nucleotides in length, and most preferably about 20-25 nucleotides in length. For a certain type of microarray or detection kit, it may be preferable to use oligonucleotides that are only 7-20 nucleotides in length. The microarray or detection kit may contain oligonucleotides that cover the known 5', or 3', sequence, sequential oligonucleotides which cover the full length sequence; or unique oligonucleotides selected from particular areas along the length of the sequence. Polynucleotides used in the microarray or detection kit may be oligonucleotides that are specific to a gene or genes of interest.

In order to produce oligonucleotides to a known sequence for a microarray or detection kit, the gene(s) of interest (or an ORF identified from the contigs of the present invention) is typically examined using a computer algorithm which starts at the 5' or at the 3' end of the nucleotide sequence. Typical algorithms will then identify oligomers of defined length that are unique to the gene, have a GC content within a range suitable for hybridization, and lack predicted secondary structure that may interfere with hybridization. In certain situations it may be appropriate to use pairs of oligonucleotides on a microarray or detection kit. The "pairs" will be identical, except for one nucleotide that preferably is located in the center of the sequence. The second oligonucleotide in the pair (mismatched by one) serves as a control. The number of oligonucleotide pairs may range from two to one million. The oligomers are synthesized at designated areas on a substrate using a light-directed chemical process. The substrate may be paper, nylon or other type of membrane, filter, chip, glass slide or any other suitable solid support.

In another aspect, an oligonucleotide may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler *et al.*) which is incorporated herein in its entirety by reference. In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array, such as those described above, may be produced by hand or by using available devices (slot blot or dot blot apparatus), materials (any suitable solid support), and

machines (including robotic instruments), and may contain 8, 24, 96, 384, 1536, 6144 or more oligonucleotides, or any other number between two and one million which lends itself to the efficient use of commercially available instrumentation.

In order to conduct sample analysis using a microarray or detection kit, the RNA or DNA from a biological sample is made into hybridization probes. The mRNA is isolated, and cDNA is produced and used as a template to make antisense RNA (aRNA). The aRNA is amplified in the presence of fluorescent nucleotides, and labeled probes are incubated with the microarray or detection kit so that the probe sequences hybridize to complementary oligonucleotides of the microarray or detection kit. Incubation conditions are adjusted so that hybridization occurs with precise complementary matches or with various degrees of less complementarity. After removal of nonhybridized probes, a scanner is used to determine the levels and patterns of fluorescence. The scanned images are examined to determine degree of complementarity and the relative abundance of each oligonucleotide sequence on the microarray or detection kit. The biological samples may be obtained from any bodily fluids (such as blood, urine, saliva, phlegm, gastric juices, etc.), cultured cells, biopsies, or other tissue preparations. A detection system may be used to measure the absence, presence, and amount of hybridization for all of the distinct sequences simultaneously. This data may be used for large-scale correlation studies on the sequences, expression patterns, mutations, variants, or polymorphisms among samples.

Using such arrays, the present invention provides methods to identify the expression of the phosphatase proteins/peptides of the present invention. In detail, such methods comprise incubating a test sample with one or more nucleic acid molecules and assaying for binding of the nucleic acid molecule with components within the test sample. Such assays will typically involve arrays comprising many genes, at least one of which is a gene of the present invention and or alleles of the phosphatase gene of the present invention. Figure 3 provides SNP information that has been found in a gene encoding the phosphatase protein of the present invention. The following variations were seen: G3114A, T4514G, A7570G, C11672G, A11897C, T14523C, C16586T, T16644C, A17969G, C18117T, C18518A, G19882A, A21465G, C21625T, C26291T, T28012C, T28030G, A33671C, A37703G and C39269G as substitutions, -20999T, -4004A as insertions and G20988- deletion. The changes in the amino acid sequence that these SNPs cause can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a base.

Conditions for incubating a nucleic acid molecule with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and

the type and nature of the nucleic acid molecule used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or array assay formats can readily be adapted to employ the novel fragments of the Human genome disclosed herein. Examples of such assays can be found in Chard, T, *An Introduction to Radioimmunoassay and Related Techniques,* Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G. R. *et al., Techniques in Immunocytochemistry,* Academic Press, Orlando, FL Vol. 1 (1 982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., *Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology,* Elsevier Science Publishers, Amsterdam, The Netherlands (1985).

The test samples of the present invention include cells, protein or membrane extracts of cells. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing nucleic acid extracts or of cells are well known in the art and can be readily be adapted in order to obtain a sample that is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention.

Specifically, the invention provides a compartmentalized kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the nucleic acid molecules that can bind to a fragment of the Human genome disclosed herein; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound nucleic acid.

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers, strips of plastic, glass or paper, or arraying material such as silica. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the nucleic acid probe, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound probe. One skilled in the art will readily recognize that the previously unidentified phosphatase gene of the present invention can be routinely identified using the sequence

information disclosed herein can be readily incorporated into one of the established kit formats which are well known in the art, particularly expression arrays.

Vectors/host cells

The invention also provides vectors containing the nucleic acid molecules described herein. The term "vector" refers to a vehicle, preferably a nucleic acid molecule, which can transport the nucleic acid molecules. When the vector is a nucleic acid molecule, the nucleic acid molecules are covalently linked to the vector nucleic acid. With this aspect of the invention, the vector includes a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, OR MAC.

A vector can be maintained in the host cell as an extrachromosomal element where it replicates and produces additional copies of the nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the nucleic acid molecules when the host cell replicates.

The invention provides vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the nucleic acid molecules. The vectors can function in prokaryotic or eukaryotic cells or in both (shuttle vectors).

Expression vectors contain cis-acting regulatory regions that are operably linked in the vector to the nucleic acid molecules such that transcription of the nucleic acid molecules is allowed in a host cell. The nucleic acid molecules can be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

The regulatory sequence to which the nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage λ, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region a ribosome binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. The person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors. Such regulatory sequences are described, for example, in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

A variety of expression vectors can be used to express a nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for example vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses, papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors may also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, e.g. cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

The regulatory sequence may provide constitutive expression in one or more host cells (i.e. tissue specific) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor such as a hormone or other ligand. A variety of vectors providing for constitutive and inducible expression in prokaryotic and eukaryotic hosts are well known to those of ordinary skill in the art.

The nucleic acid molecules can be inserted into the vector nucleic acid by well-known methodology. Generally, the DNA sequence that will ultimately be expressed is joined to an expression vector by cleaving the DNA sequence and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial cells

include, but are not limited to, *E. coli*, *Streptomyces*, and *Salmonella typhimurium*. Eukaryotic cells include, but are not limited to, yeast, insect cells such as *Drosophila*, animal cells such as COS and CHO cells, and plant cells.

As described herein, it may be desirable to express the peptide as a fusion protein. Accordingly, the invention provides fusion vectors that allow for the production of the peptides. Fusion vectors can increase the expression of a recombinant protein, increase the solubility of the recombinant protein, and aid in the purification of the protein by acting for example as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes include, but are not limited to, factor Xa, thrombin, and enterophosphatase. Typical fusion expression vectors include pGEX (Smith *et al.*, *Gene 67*:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, *Gene 69*:301-315 (1988)) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology 185*:60-89 (1990)).

Recombinant protein expression can be maximized in host bacteria by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein. (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example *E. coli*. (Wada *et al.*, *Nucleic Acids Res. 20*:2111-2118 (1992)).

The nucleic acid molecules can also be expressed by expression vectors that are operative in yeast. Examples of vectors for expression in yeast e.g., *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, *EMBO J. 6*:229-234 (1987)), pMFa (Kurjan *et al.*, *Cell 30*:933-943(1982)), pJRY88 (Schultz *et al.*, *Gene 54*:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

The nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith *et al.*, *Mol. Cell Biol. 3*:2156-2165 (1983)) and the pVL series (Lucklow *et al.*, *Virology 170*:31-39 (1989)).

In certain embodiments of the invention, the nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples of mammalian

expression vectors include pCDM8 (Seed, B. *Nature 329*:840(1987)) and pMT2PC (Kaufman *et al.*, *EMBO J. 6*:187-195 (1987)).

The expression vectors listed herein are provided by way of example only of the well-known vectors available to those of ordinary skill in the art that would be useful to express the nucleic acid molecules. The person of ordinary skill in the art would be aware of other vectors suitable for maintenance propagation or expression of the nucleic acid molecules described herein. These are found for example in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

The invention also encompasses vectors in which the nucleic acid sequences described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to all, or to a portion, of the nucleic acid molecule sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

The invention also relates to recombinant host cells containing the vectors described herein. Host cells therefore include prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

The recombinant host cells are prepared by introducing the vector constructs described herein into the cells by techniques readily available to the person of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Host cells can contain more than one vector. Thus, different nucleotide sequences can be introduced on different vectors of the same cell. Similarly, the nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the nucleic acid molecules such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced or joined to the nucleic acid molecule vector.

In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral

vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication will occur in host cells providing functions that complement the defects.

Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be contained in the same vector that contains the nucleic acid molecules described herein or may be on a separate vector. Markers include tetracycline or ampicillin-resistance genes for prokaryotic host cells and dihydrofolate reductase or neomycin resistance for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait will be effective.

While the mature proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell- free transcription and translation systems can also be used to produce these proteins using RNA derived from the DNA constructs described herein.

Where secretion of the peptide is desired, which is difficult to achieve with multi-transmembrane domain containing proteins such as phosphatases, appropriate secretion signals are incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

Where the peptide is not secreted into the medium, which is typically the case with phosphatases, the protein can be isolated from the host cell by standard disruption procedures, including freeze thaw, sonication, mechanical disruption, use of lysing agents and the like. The peptide can then be recovered and purified by well-known purification methods including ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

It is also understood that depending upon the host cell in recombinant production of the peptides described herein, the peptides can have various glycosylation patterns, depending upon the cell, or maybe non-glycosylated as when produced in bacteria. In addition, the peptides may include an initial modified methionine in some cases as a result of a host-mediated process.

Uses of vectors and host cells

The recombinant host cells expressing the peptides described herein have a variety of uses. First, the cells are useful for producing a phosphatase protein or peptide that can be further

purified to produce desired amounts of phosphatase protein or fragments. Thus, host cells containing expression vectors are useful for peptide production.

Host cells are also useful for conducting cell-based assays involving the phosphatase protein or phosphatase protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a native phosphatase protein is useful for assaying compounds that stimulate or inhibit phosphatase protein function.

Host cells are also useful for identifying phosphatase protein mutants in which these functions are affected. If the mutants naturally occur and give rise to a pathology, host cells containing the mutations are useful to assay compounds that have a desired effect on the mutant phosphatase protein (for example, stimulating or inhibiting function) which may not be indicated by their effect on the native phosphatase protein.

Genetically engineered host cells can be further used to produce non-human transgenic animals. A transgenic animal is preferably a mammal, for example a rodent, such as a rat or mouse, in which one or more of the cells of the animal include a transgene. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal in one or more cell types or tissues of the transgenic animal. These animals are useful for studying the function of a phosphatase protein and identifying and evaluating modulators of phosphatase protein activity. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians.

A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the phosphatase protein nucleotide sequences can be introduced as a transgene into the genome of a non-human animal, such as a mouse.

Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. This includes intronic sequences and polyadenylation signals, if not already included. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the phosphatase protein to particular cells.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for

production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of transgenic mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene can further be bred to other transgenic animals carrying other transgenes. A transgenic animal also includes animals in which the entire animal or tissues in the animal have been produced using the homologously recombinant host cells described herein.

In another embodiment, transgenic non-human animals can be produced which contain selected systems that allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al. PNAS 89*:6232-6236 (1992). Another example of a recombinase system is the FLP recombinase system of *S. cerevisiae* (O'Gorman *et al. Science 251*:1351-1355 (1991). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein is required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al. Nature 385*:810-813 (1997) and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring born of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

Transgenic animals containing recombinant cells that express the peptides described herein are useful to conduct the assays described herein in an *in vivo* context. Accordingly, the various physiological factors that are present *in vivo* and that could effect substrate binding, kinase protein activation, and signal transduction, may not be evident from *in vitro* cell-free or cell-based assays. Accordingly, it is useful to provide non-human transgenic animals to assay *in vivo* phosphatase protein function, including substrate interaction, the effect of specific mutant phosphatase proteins on phosphatase protein function and substrate interaction, and the effect of

chimeric phosphatase proteins. It is also possible to assess the effect of null mutations, that is mutations that substantially or completely eliminate one or more phosphatase protein functions.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

Claims

That which is claimed is:

1. An isolated peptide consisting of an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence shown in SEQ ID NO:2;

(b) an amino acid sequence of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) an amino acid sequence of an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3; and

(d) a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids.

2. An isolated peptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence shown in SEQ ID NO:2;

(b) an amino acid sequence of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) an amino acid sequence of an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3; and

(d) a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids.

3. An isolated antibody that selectively binds to a peptide of claim 2.

4. An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence shown in SEQ ID NO:2;

(b) a nucleotide sequence that encodes of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

5. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence shown in SEQ ID NO:2;

(b) a nucleotide sequence that encodes of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

6. A gene chip comprising a nucleic acid molecule of claim 5.

7. A transgenic non-human animal comprising a nucleic acid molecule of claim 5.

8. A nucleic acid vector comprising a nucleic acid molecule of claim 5.

9. A host cell containing the vector of claim 8.

10. A method for producing any of the peptides of claim 1 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

11. A method for producing any of the peptides of claim 2 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

12. A method for detecting the presence of any of the peptides of claim 2 in a sample, said method comprising contacting said sample with a detection agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide.

13. A method for detecting the presence of a nucleic acid molecule of claim 5 in a sample, said method comprising contacting the sample with an oligonucleotide that hybridizes to said nucleic acid molecule under stringent conditions and determining whether the oligonucleotide binds to said nucleic acid molecule in the sample.

14. A method for identifying a modulator of a peptide of claim 2, said method comprising contacting said peptide with an agent and determining if said agent has modulated the function or activity of said peptide.

15. The method of claim 14, wherein said agent is administered to a host cell comprising an expression vector that expresses said peptide.

16. A method for identifying an agent that binds to any of the peptides of claim 2, said method comprising contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the peptide.

17. A pharmaceutical composition comprising an agent identified by the method of claim 16 and a pharmaceutically acceptable carrier therefor.

18. A method for treating a disease or condition mediated by a human phosphatase protein, said method comprising administering to a patient a pharmaceutically effective amount of an agent identified by the method of claim 16.

19. A method for identifying a modulator of the expression of a peptide of claim 2, said method comprising contacting a cell expressing said peptide with an agent, and determining if said agent has modulated the expression of said peptide.

20. An isolated human phosphatase peptide having an amino acid sequence that shares at least 70% homology with an amino acid sequence shown in SEQ ID NO:2.

21. A peptide according to claim 20 that shares at least 90 percent homology with an amino acid sequence shown in SEQ ID NO:2.

22. An isolated nucleic acid molecule encoding a human phosphatase peptide, said nucleic acid molecule sharing at least 80 percent homology with a nucleic acid molecule shown in SEQ ID NOS:1 or 3.

23. A nucleic acid molecule according to claim 22 that shares at least 90 percent homology with a nucleic acid molecule shown in SEQ ID NOS:1 or 3.

```
   1  ATGGAGGACG TGAAGCTGGA GTTCCCTTCC CTTCCACAGT GCAAGGAAGA
  51  CGCCGAGGAG TGGACCTACC CTATGAGACG AGAGATGCAG GAAATTTTAC
 101  CTGGATTGTT CTTAGGCCCA TATTCATCTG CTATGAAAAG CAAGCTACCT
 151  GTACTACAGA AACATGGAAT AACCCATATA ATATGCATAC GACAAAATAT
 201  TGAAGCAAAC TTTATTAAAC CAAACTTTCA GCAGTTATTT AGATATTTAG
 251  TCCTGGATAT TGCAGATAAT CCAGTTGAAA ATATAATACG TTTTTTCCCT
 301  ATGACTAAGG AATTTATTGA TGGGAGCTTA CAAATGGGAG GAAAAGTTCT
 351  TGTGCATGGA AATGCAGGGA TCTCCAGAAG TGCAGCCTTT GTTATTGCAT
 401  ACATTATGGA AACATTTGGA ATGAAGTACA GAGATGCTTT TGCTTATGTT
 451  CAAGAAAGAA GATTTTGTAT TAATCCTAAT GCTGGATTTG TCCATCAACT
 501  TCAGGAATAT GAAGCCATCT ACCTAGCAAA ATTAACAATA CAGATGATGT
 551  CACCACTCCA GATAGAAAGG TCATTATCTG TTCATTCTGG TACCACAGGC
 601  AGTTTGAAGA GAACACATGA AGAAGAGGAT GATTTTGGAA CCATGCAAGT
 651  GGCGACTGCA CAGAATGGCT GA
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FEATURES:
Start codon: 1
Stop codon: 670

cDNA Sequence:

```
   1  AACACCACGC GTCCGGCAGC GGCATGGCGG CCGGGTGTAA GACGCCCGAC
  51  CCTCCTCTTC CCTGTCTTCG CCGCCGCCGC TGCTGGAGTC ACTGGGACCC
 101  TGTAGTCTGC GTGTGTTAGT TGTAATCCCG CCGCCCTCCT GTCAGCCCTC
 151  CGCTCCGCCG GCCCTCCTTC CTTCCGCCGC CGCAGCCAGC CCGAGGGTCG
 201  GCCGGCTGTG TAACACTCTC CCACCCCACC CACCAGCCCG CGGGCCAGCA
 251  CCATGGAGGA CGTGAAGCTG GAGTTCCCTT CCCTTCCACA GTGCAAGGAA
 301  GACGCCGAGG AGTGGACCTA CCCTATGAGA CGAGAGATGC AGGAAATTTT
 351  ACCTGGATTG TTCTTAGGCC CATATTCATC TGCTATGAAA AGCAAGCTAC
 401  CTGTACTACA GAAACATGGA ATAACCCATA TAATATGCAT ACGACAAAAT
 451  ATTGAAGCAA ACTTTATTAA ACCAAACTTT CAGCAGTTAT TTAGATATTT
 501  AGTCCTGGAT ATTGCAGATA ATCCAGTTGA AAATATAATA CGTTTTTTCC
 551  CTATGACTAA GGAATTTATT GATGGGAGCT TACAAATGGG AGGAAAAGTT
 601  CTTGTGCATG GAAATGCAGG GATCTCCAGA AGTGCAGCCT TTGTTATTGC
 651  ATACATTATG GAAACATTTG GAATGAAGTA CAGAGATGCT TTTGCTTATG
 701  TTCAAGAAAG AAGATTTTGT ATTAATCCTA ATGCTGGATT TGTCCATCAA
 751  CTTCAGGAAT ATGAAGCCAT CTACCTAGCA AAATTAACAA TACAGATGAT
 801  GTCACCACTC CAGATAGAAA GGTCATTATC TGTTCATTCT GGTACCACAG
 851  GCAGTTTGAA GAGAACACAT GAAGAAGAGG ATGATTTTGG AACCATGCAA
 901  GTGGCGACTG CACAGAATGG CTGACTTGAA GAGCAACATC ATAGAGTGTG
 951  AATTTCTATT TGGGAAGGAG AAAATACAAG AGAAAATTAT AATGTAAAAT
1001  GGTAAAAACA TAAGTAGTTT TTTTTTCAAT TACATGTTGC TTCCAGACAT
1051  ACTTCTCTGC AACTTGTTGA GCAACATTTT AAGATGTTGG ACTTCTGCAA
1101  TAGATGACAC TGATGGTTTT ACTCCTTTTT TTTAAAAACA CATGCGCGCG
1151  CACACACACA TGCTTTACAA GTTTTATTAT AAACCAAGAA TTTTGGACTT
1201  GCAAAAAAAA AAAAAAAA
```

FEATURES:

Start codon: 253
Stop codon: 922

FIGURE 1

Homologous proteins:
Top 10 BLAST Hits

gi|2137698|pir||I49365 protein tyrosine phosphatase - mouse >gi...	462	e-129
gi|2137697|pir||I49364 protein tyrosine phosphatase - mouse >gi...	356	1e-97
gi|1842088 (U87169) tyrosine phosphatase-like protein homolog h...	141	5e-33
gi|4758206|ref|NP_004409.1|| dual specificity phosphatase 2 >gi...	94	9e-19
gi|4758212|ref|NP_004411.1|| dual specificity phosphatase 8 >gi...	93	2e-18
gi|6679156|ref|NP_032774.1|| neuronal tyrosine/threonine phosph...	93	2e-18
gi|4758204|ref|NP_004408.1|| dual specificity phosphatase 1 >gi...	92	5e-18
gi|1050849|emb|CAA58710| (X83742) MAP kinase phosphatase [Xenop...	91	8e-18
gi|4150963|emb|CAA77232| (Y18620) DsPTP1 protein [Arabidopsis t...	90	1e-17
gi|6714641|dbj|BAA89534.1| (AB036834) MAP kinase phosphatase [D...	90	1e-17

EST

gi|2059098|gb|AA404320.1|AA404320 zw36g07.s1 Soares_total_fetus...	761	0.0
gi|2810244|gb|AA761314.1|AA761314 nz21c05.s1 NCI_CGAP_GCB1 Homo...	630	e-178
gi|1472397|gb|AA011350.1|AA011350 zi01b04.s1 Soares_fetal_liver...	607	e-171
gi|1230791|gb|N73506.1|N73506 za49c05.s1 Soares fetal liver spl...	597	e-168
gi|4389706|gb|AI497724.1|AI497724 ti50c07.x1 NCI_CGAP_Lym12 Hom...	379	e-103

EXPRESSION INFORMATION FOR MODULATORY USE:

gi|2059098|gb|AA404320.1	Human total fetus
gi|2810244|gb|AA761314.1	Human Germinal B cell
gi|1472397|gb|AA011350.1	Human fetal liver
gi|1230791|gb|N73506.1	Human fetal liver spleen
gi|4389706|gb|AI497724.1	Human Lymph node

PCR-BASED TISSUE SCREENING PANEL:
Human fetal brain, human Brain, human heart, human liver, human lung, human placenta, human thyroid.

FIGURE 1.

```
   1  MEDVKLEFPS LPQCKEDAEE WTYPMRREMQ EILPGLFLGP YSSAMKSKLP
  51  VLQKHGITHI ICIRQNIEAN FIKPNFQQLF RYLVLDIADN PVENIIRFFP
 101  MTKEFIDGSL QMGGKVLVHG NAGISRSAAF VIAYIMETFG MKYRDAFAYV
 151  QERRFCINPN AGFVHQLQEY EAIYLAKLTI QMMSPLQIER SLSVHSGTTG
 201  SLKRTHEEED DFGTMQVATA QNG
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FEATURES:
Functional domains and key regions:

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[1] PDOC00005 PS00005 PKC_PHOSPHO_SITE
Protein kinase C phosphorylation site
201-203 SLK

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[2] PDOC00006 PS00006 CK2_PHOSPHO_SITE
Casein kinase II phosphorylation site
205-208 THEE

---

[3] PDOC00007 PS00007 TYR_PHOSPHO_SITE
Tyrosine kinase phosphorylation site
Number of matches: 2 1 15-23 KEDAEEWTY 2 142-149 KYRDAFAY

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[4] PDOC00008 PS00008 MYRISTYL
N-myristoylation site
Number of matches: 2 1 123-128 GISRSA 2 197-202 GTTGSL

Membrane spanning structure and domains:

Helix	Begin	End	Score	Certainty
1	123	143	0.626	Putative

FIGURE 2

BLAST Alignment to Top Hit:

```
>gi|2137698|pir||I49365 protein tyrosine phosphatase - mouse
          >gi|1063626|gb|AAA87037.1| (U34973) protein tyrosine
          phosphatase-like [Mus musculus]
          Length = 223

 Score =  444 bits (1131), Expect = e-124
 Identities = 214/223 (95%), Positives = 221/223 (98%)

Query: 1   MEDVKLEFPSLPQCKEDAEEWTYPMRREMQEILPGLFLGPYSSAMKSKLPVLQKHGITHI 60
           MEDVKLEFPS+PQCK+DAEEWTYPMRREMQE+LPGLFLGPYSSAMKSKLP+LQKHGITHI
Sbjct: 1   MEDVKLEFPSVPQCKDDAEEWTYPMRREMQEVLPGLFLGPYSSAMKSKLPILQKHGITHI 60

Query: 61  ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQMGGKVLVHG 120
           ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQ GGKVLVHG
Sbjct: 61  ICIRQNIEANFIKPNFQQLFRYLVLDIADNPVENIIRFFPMTKEFIDGSLQNGGKVLVHG 120

Query: 121 NAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI 180
           NAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI
Sbjct: 121 NAGISRSAAFVIAYIMETFGMKYRDAFAYVQERRFCINPNAGFVHQLQEYEAIYLAKLTI 180

Query: 181 QMMSPLQIERSLSVHSGTTGSLKRTHEEEDDFGTMQVATAQNG 223 .
           QMMSPLQIERSL+VHSGTTGS+KRTHEE+DDFG MQVATAQNG
Sbjct: 181 QMMSPLQIERSLAVHSGTTGSVKRTHEEDDDFGNMQVATAQNG 223
```

Hmmer search results (Pfam):

Scores for sequence family classification (score includes all domains):

Model	Description	Score	E-value	N
PF00782	Dual specificity phosphatase, catalytic doma	221.5	1.2e-62	1

FIGURE 2

```
   1  TTGAAATCCA AAAATATCTG AAGCTACATT TGGACCCCTG TAAATAATGT
  51  AATGTATAAG GATTTTTCCA AAATAAGTCT TAATTTCAGT TTTCATATAT
 101  CAACAAAAAG GTACTATTAG GAGTACATAG TTGCCACACT TGAGACATAT
 151  TCCAAATGCA TACACCTAAC GGTACTACTA TTACAGAACA GCACATTCTA
 201  ATCCACATAT ACACGAGTTT TAATTAAATT TAGCACTATG TCTATAATCA
 251  GAATGAATAC CTGGAATACA TGTTTCTAGC AGGAATATTT GTTAGCAGCT
 301  TTAAGGTACT TGAAATCACC ATAATCATTT CTATTTTAAA TTTAAATTTC
 351  ACTACTGGGG TAAATTCCAT GAGGGAAGGT TGTGGCTATG AATTTTTATT
 401  TATTCTTTTT CTTTTGTGGT AAATATGGAG AACTTACCAA ATCTCTTATA
 451  TAGCCTGGCT GTAGATGGCA ATGCGAGGAA AGAAAAAGGA AGCAGAAAGA
 501  AAAAAAAAGG CAATCAGAAA AAATGGCAAC GAAGCAAAGA AAAAGTTGCG
 551  GTCACCTGCA AACCAAAATT CCAGCCAAAA GTCATGCAAA AAACTACTTT
 601  AGGTAGAAAC CAAGCAAAGT AAATGCAAGA ATGAAAAATG AAAATGAGGA
 651  AGCAGCAATT ACTTTCCATT TAGAACACTG AGAAACACTC CACATTATTT
 701  TAGAATGTTA AATGTTGCTA AAGAACCTAA GGGTAGAAAT TTGTAGGGAG
 751  AAGATAAAAA GAGCAAATAT TTCTTTCCCC CTACATCGTG TACCCAGTTA
 801  CATCGTGTAC CCAGTTCTCA CCGGTTAAGG TAAAGCCAAT TATTTTAGTA
 851  GCAAAATAAA AGTATCCAAA AGCCTTTAAA GTCTTCTCAG ATTTAGTCAG
 901  ATAATATGAT CCATGCACTG CTTTTCAGAA ATAAGAATTT GAAGGCATAA
 951  AATAAGTGCA GTGCCCATCT GTTTCTTTTT TTACACAAGA AAAGCAAACC
1001  CCTCAGTTAC CATGTGTTTT TTGCATCCTT TTTCCTGGAA GGGAAAACAA
1051  AGAGATGCCG TATACTACAT GAGGAATTTC GGCTTTATGG CATTAGTCAT
1101  TTCCATTTAG ATTAACATAA ATCAACATAT AGAATAATTC TTCAAAATTT
1151  AAAAATCCAG TTTGAGAGTC ATATTTATTT AAAAATACCC ACAGCATGTT
1201  TAGTTAATAT ATATATAATT GAAGGGAATT AAAGTAGGTT AAATACAACA
1251  GGTTATTTTG ATAGACCCAA AAGAAAACTA CGAGTCTATG CCCAGGTAGG
1301  GAAGAATGTC CTTGTGGCCT GCACATCTTC CTACAGCCTC CAGAACGCAA
1351  CTGGATACAG CTTAATAATT ACTGAGCACT ATGTCCAGTG TGACTAGTGT
1401  GGTATCTGAC ACACAGTAGC AACTAAACTT CTGAATGTCA CTACTTACTA
1451  GGCACCAGGG CAATAACATC ATGGTCGCTA TTCTCTGGAA ACAATTTTTT
1501  TTTCTGACAC GGAGTTTCAC TCTTGTTGCC CAGGCTGGAG TGCAATGGCG
1551  CCATCTTGGC TCACTGCAAC CTCCACCTCC CAGGTACAGG TGATTCTCCT
1601  GCCTCAGCCT CCCAAGTAGC TGGCATTATA GGCGTGCACC ACCATGCCTG
1651  GCTAATTTTT GTAGTTTTAG TAGAGATGGG GTTTCACCAT GTTGGCCAGG
1701  CTGGTCTCGA ACTCCTGACC TCAGGTGTTC CACTCACCTC GGCCTCCCTA
1751  AGTGCTGGGA TTACAGGTGT GAGCCACCGC ACCTAGCCCA ACACAACTAT
1801  TCAATAGAAA TTTCTCTCTC GGTCAGGCAT GGTGGCTCAC GCCTGTAATC
1851  CCAGCACTCT GGGAGGCTGA GGTGGGTGGA TCATCTGAGG TCAGGAGTTC
1901  AAGACCAGCC TGCCAATACA GTGAAACCCC ATCTCTTCTA AAAGTACAAA
1951  AATTAGCCAG GTGTGGTGGT GGCGCCTGTA GTCCCAGCTA CTCAGGAGGC
2001  TGAGACAGGA GAATCTCTTG TACCCGGGAG GCAGAGGTTG CAATGAGCCA
2051  AGATCATGCC ATTGCACTCC AGCCTGGGCA ACAGACTCTG TCTCAAAAAA
2101  AAAGAAATTT CTCTCTTAAG TTACTGGTAC TATAAGTAAT TTAAATTGGA
2151  CTTTCAGATC TTCAATTTCT CTAGTCTCTA CTTTTCTTCC TTGAATCAGT
2201  CTTGAGAGCA GAACATACTG TTCTTTAAAA GCTGCCGTGG CAAAATGCCA
2251  ACAGATAAAA ATTGTATATA CCTTTTCTCT TGGTATGTTG TCAAATCCAT
2301  CCCCCATTTT AGAATTATTT TGTGTTGTAT TTTCAAATGC AAACTAGTAT
2351  AGATCTTTTG AGTTGTGTTT TTTGTTTATA TGTTCATTTG ACTTAACTGA
2401  TTTTTTTGTG GTATAATTTT TCATTGAGGT ATAATTACAT TAAAAAAATG
2451  TAGATTCTTA AGTGTACATT TCAAATATGT TTGGACAAGT TATATATCTG
2501  TGTAACCATC ACCCCAATCA AGTGTGTGGT TTATTTAAAA AACATTATTT
2551  GAAATTTTTT AGATTTAAGA GATCTTAAAT CTACCTGGAG CAAAACCTCT
2601  TAATATAAAT GGTTTTACCT AGCATGGAAG TCTAGGTCTA TTAAGAATTA
2651  TGATGTGTAC ACCTAACTAA GGTGATATTT GACTTAGAGT ATTTGAAAGT
2701  ACATTAAAAA TCTTGACTAA CTTTTTAAGA AAGATTTAAC TTCTTTTCTA
2751  GGTGATAGAA TTACCTCTTA CAAACCCAGA GTTATTTCAG CGTGTAGGAA
2801  TAATACCTCC AAAAGGCTGT TTGTTATATG GACCACCAGG TTGGTATTGA
2851  ATTATTTCTA CTCCACCAAT AAGATAAATG AATTAAGGAA TTAAAAAAAA
2901  AAAGACAATT TTTTTATTTT TATTTTTTTG AGACACGGTC TCACTCTGTT
2951  GCCCAGGCTG TAGTGCAGTG GCACAATCTG GGCTAACTGC AACCTCTGCC
3001  TTCCGGGCTC AAGTGATTCT CCCACCTCAG TCTCCCACGT AGCTGGGACT
3051  GCAGGCGTGC ATCACCATGT CTGGTTAATT TTTGTATGTT TTGTAGAGAA
3101  GCAATTTTGC CATGTTGCTC AGGCTATCTC AAACTCCTGG ACTCAAGCGA
3151  TCTGCCCACC TTAGCCTCCC AAAATGTTGG GATTACAAGC ATAAACCACT
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FIGURE 3

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3201  GCGCCTGGCC ATAAGGTGGA AATTTGATGT GGGCAGTTCC AACTTCTCCT
3251  CTCTTCAGAG TGAGAATGAG ATAGGATATT TATGTCTACT GTTCTTTGAG
3301  GCATGCTTAG TGCATTTGTG CCTCACAGTA CATTTATCTT AACAGGCCAT
3351  GTGATTCTAG TGCAACAGTC CTCAAATTGT GGTTCACAGA CCCAGAGGTG
3401  CTTTCATGGA CTCTGTAAGG TCAAAACTAC TTTATAATAC TGAAATGTTA
3451  AGCCAGGCGC AGTGGCTCAC ACCTGTAATC CCAGCACTTC GGGAGGCCGA
3501  GGCAGGCAGA TCACCAGAGG TCAGGAGTTT GAGAGCAGCC TGGCCAACCA
3551  ACATGATGAA ACCCTGTCTC TACTAAAAAT ACAAAAATGA GCCAGGCGTG
3601  GTGGCGTGCA CCTGTAATCC CAGCTACTCG GGAAGCTGAG GCAGGAGAAT
3651  TGCTTGAACC TGGGAGGCAG AGGTTGCAGT GAGCCGAGAT TGCCCCACTG
3701  CACTCCAGCC TGGCTGACAG AGTGAGACTC CTTCTCAAAA AAAAAAAAAA
3751  AAAAAAAAAA ATTTTTTATA TAAAGCAAAT GTACCTATAG CATACTGCTT
3801  GACATATGTA GCCCCACAAT GACACAAAAC AAAAAACTAA AATGTTGTTT
3851  GGCTCTTCCA CTGTGTTGAC ATTTGTGCTG ATGGTGCAAG AGCACCATGG
3901  GTAAAATTAA ATTACTTGCA CTGTAGTGTG AATCAGCATT AGTGGCATGA
3951  AACGGTGCTA GTTAGTAGCC ATTGCGTTCT TGACTGCCAC ATACTTGCAG
4001  TGTAAAAAAA AAAAAAAGTC AGTTTCACTA TAAAGTCCTT GGTGAAACAG
4051  TAAAAATTAT TAATTTTGTT AAATCTTCAT CTTTGGGTAA TATTTTGTGT
4101  TCTTCATGAT AAAAGGGAAA ATAAATATAA AGTACTGCTG CATATTGAAT
4151  AAGATAGTTG TCTTTAGGAA AAGCACTTGT GCAGTTATTT AAGTTGCCAG
4201  CTGAATTCAT TGCTTTTTAT GGAATACTAT TTTTGCTTGA ATGGACCATT
4251  TACAGATATG CTGTGATTAT CAGACTGGTT ATTGGTTATT AGTTATTGAT
4301  TACTCAAGAC TGGTTTTTGG TTATTTGGCG CACATTTTTT CCAAAGCGAA
4351  CAAATTAAGC CTGTCATGTT AAACAACTGA CACCATCTAT TGCCATTGAT
4401  AAAATATGAA ATGTCAAGTG AAAATTAGAA TTTTTAGAAA CATATATCTG
4451  GCACTATGTG GTTGAAGCTT TTTCTTTTTT TCTTTTCTTT TCTTTTTTTT
4501  TTTTTTGATA AGGTGTTACT CTGTTACCCA GGCTGGAGTG CAGTGGCGTG
4551  ATCATCCTGG CTCGCTGCAA CTTCTGCCTC TTGGGCTCAG GTGATTCTTC
4601  CACCTCAGCC TCCTGAGTAG CTGGTACTAC AGGTGTGTGC CACCATGCCA
4651  GGCTAATTTT TGTGTTTTTA GTAGAGGCAG GGTTTTGCCA TGTTGCCCAG
4701  GCTGGTCTTG AATTCCTGGG CTCAAGCAAC CCGCCCACCT CAGCCTCCCA
4751  AAGTGCTGGG ATTACAGGCA TGAGCCACAA TGTCCAGCCA CGGCAGCTTT
4801  CTAATATATT AATACTTAAA GACTTTTCTG ATGAGATAAG TGGTGAGAAT
4851  AACAAAAATT TTTTATAATG TGTGGTGGAA AATGTCAACA TTTGGAAGAT
4901  TTGCATAACT CAACCAGTAG TTTCCAAATA ATCAATGCTT GATATTAAAA
4951  TATTCATAAG TAAAAGATCC AGTCAGTGCA CAGGATAGAC CAATGTATTT
5001  TAATGTAACA GAAGTTTCTG TCATAGTCCA TGTTGTAAGT AGATAGCTAT
5051  TATAAAAAAG ACAAAAGTGT TTGCAAGATG TAGAGAAAAG AGAAAGAACC
5101  CTTGTACACT ACTGGTGGGA ATGTAAATTA GCACAGCCAT TTTTGAAAAC
5151  ATGGAGGTTC CTCAAAAAAC TAAAAATAGA ATTACCATAT GATTCAGCAA
5201  TCCCACTTCT GGGTTTATAT CTAAAGGAAT TGAAATCAGT GTGTCAGAGA
5251  TAGCTGCACT CCCATGATTA TTTCACAATA GCCAAGATAT AGAAACAGCC
5301  TAAAAATTGC CCATCAATGG ATGAATGGAT AAAGAAAATG TGGTAGCCGG
5351  GTGCAGTGGC TCATACCTGT AGTGCCAACA CTTTGGGAGG CCGAGGCGGG
5401  CGGATCACCT GAGGTCGGGA GTTCGAGACC AGCCTGACCA ACATGGAGAA
5451  ACCCCGTCTC TGCTGAAAAT ACAAAATTAG CTGGGTGTAG TAGTTCATGC
5501  CTGTAATCCC AGCTACTCGG GAGGCAGAGG CAGGAGAATC ACTTGAACCT
5551  GGGAGGCAGA GGTTGCAGTG AGCTGAGATC ATGCCATTGC ACTCCAGCCT
5601  GGGCAACAAG AGTGAAACTC CATCTCAAAA AAAAAAGAAA AAGAAATGTG
5651  GTAAATACAC ACATTGGAAT ACTATTCAGC CTTAAAAAAG GAAACTCTGT
5701  CATTTGTGAC AATATGGATG AATCTAGAGG ATGTTATACT AAGTGAAATA
5751  AGCCAGACAC AGAAAGACAG TTACCACATA ATCTCATTTT CATGTGGAAT
5801  CTTAAAAAAT TGAACTCGTA GAAACCAAGA GTAGAATGGT GGTTACCAGA
5851  AGTTGTGGTG GTGTATGGGG ATAGGGGAGA TGTTGGTCAA AGGATATAAA
5901  GTTCACTTAG ACAGGAGGAA TAAGTTCTAG GTGACATATT GCATAGCATG
5951  GTGACTATAA TTAATAATGT ATTAGCTATT TCAAAATTGC TAAAAGTAGA
6001  TTTTAAATGT TCTAACCACA AAGTAATGCT AAGCATGTGA GGCGATGGAT
6051  ATGTTGATTT GCCTGATTTA ATCATTCTTC AATATATACA TGTATCATAA
6101  TTTAACCCAT AAATATACAA TTTATTTGTC AATTTAAAAT AGATTTTAAA
6151  AATTATAACA TTTTGATTAA AATTTTAATG TTGACAGCAG AAGTACTTTG
6201  GAATTTTTTT TTTTTTTTTT TTTTTTGAGA CAGAGTCTTG CTCTGTCACC
6251  CAGGCTGGAG TGCAGTGGCG AGATTATAAG CTCACTGCAA CCCCCACCTC
6301  CCGGATTCAA GCGATTCTCC TGCCTCAGCC TCCCCAGTAG GTGGGACTAC
6351  AGGCATGTGC CACCACGCTC AGCTAATTTT TTGTATTTTT AGTAGAGACG
6401  GGGTTTCACT GTGTTTCGAT CTCCTGACCC TGTGATCTGC CCGCCTCAGC
```

FIGURE 3

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6451  CTCCCAAAGT GCTGGGATTA CAGGTGTGAG CCACCACACC TGGCCAAGTA
6501  CTTTGGAATT TTAAATGAAA ATTCTATTTA GGATTTAGCT TTCATTTTGG
6551  AAAATTTACT TGCCAAACGA TTATATTCTT AAAAGGATTT TAAAAATTTG
6601  TTTCACATAG GCCGGGTGCG GTGGGTTCTG CCTGTAATCC CAGCACTTTG
6651  GGAGGCTGAA GTGGCAGGAT CACCTGAGCC CAAGAGTTCA AGACCAGCAT
6701  GCGCCAACAC AGAGAGACCC CGTCTCTGAA AAACAAACAG ACAAACAAAA
6751  AACTTAGCTG TGCGTGATGG CACATGCCTG TCATCCCAGC TACTTGGGAG
6801  GCTGAGGTGG GAAAATCGCT TAGGTCTGGG AGGTCAAGGT TGCAGTGAGC
6851  TGTGATCTCG CCACACTCCC AGCCTAGGTG ACAGAGTGAT TGCCTGTCTC
6901  AAAACAAATT TTTTTCTACC TTACCATCTA ATTAAGACTT CTTTTGTCAT
6951  TCTTAGGTAC GGGAAAAACA CTCTTGGCAC GAGCCGTTGC TAGCCAGCTG
7001  GACTGCAATT TCTTAAAGGT AAAGGGAAGA TTATTTTGTA CTTATTGAAA
7051  TTTAATTTTA CTTGAATTAT CTTATATTTA CCTTACTGTT TTTCCTTTAA
7101  TCAGGTTGTA TCTAGTTCTA TTGTAGACAA GTACATTGGT GAAAGTGCTC
7151  GTTTGATCAG AGAAATGTTT AATTATGCTA GAGATCATCA ACCATGCATC
7201  ATTTTTATGG ATGAAATAGA TGCTATTGGT AAGAATAACA CCCTTGTTGA
7251  AAGTTTTAGG ACTTTTTTTT AAATGTAAAA GAACCTTTTT CCCTCTCTTA
7301  ATCTGTAATT GTGACTTGTA TGAAGTAGAT ACCACAATGA ATCAGATGTT
7351  AGTTTAACCA ATTTTAATAA ATAACCTTTC ATGGCCGGGT GTGGTGGCTC
7401  ATGCCTGTAA TCCCAGCACT TTGAGAGGCC AAGGTGGGCA GATCACCAGG
7451  TCAGGAGATC GAGACCATCT GGCCAACATG GTGAAACCCT GTCTCTACTA
7501  AAAATACAAA AATTAGCTGG ATGTGGTGGC ACATGCCTGT AATCCCAGCT
7551  ACTGAGGAGG CTGAGGCACG AGAATCGCTT GAACCCAGGA GACGTAGGTT
7601  GCAGTGAGCC GAGATCACAC CACTGCACTC CAGCCTGGCG ACAGAGCGAG
7651  ACTCCGTCTC AATAAATAAC CTTTCACTTT AACAAAATGA GAAATGTTAC
7701  ACCAAAATCA AGTCTAACTT TGTCAGCATA ATTCTTGCTC TTTAATTTTC
7751  ATCTTAATGT TTTAAGCCAC AGACTGTTAT GTTCTGTTTT CTTAAATGAT
7801  GGTTGTAGAG GAAAAGAGTA ATGCATATAA ATTTCCAAAT CTACTATCTT
7851  AGGTGGTCGT CGGTTTTCTG AGGGTACTTC AGCTGACAGA GAGATTCAGA
7901  GAACGTTAAT GGAGGTAATA TTTGGTAAAG GGGGTTTATA AAGAAACCAA
7951  TGTTTATTAA ATGAAGAACT GAACATTGCA TATTTGATAG TCAAAATATA
8001  TAGAACATTT TAAATGAAAT ATGAAATTTG AAAATATTGT CAGGAACAAA
8051  CATGTTTCTC TATCACAAAC TCTAAGCAAA ATGACTACTG GAAAATAAGG
8101  CTATCTGCCA AATTCCATTT GGTATACACC TGTACTATTC TGTGTTTTTT
8151  TGAGTAGATC AGTCATTCAT ATATTTAAAT TCTTATGAAT GTGATCTTGC
8201  GGTAGTTTTA TGAAGACATT TTTTGTAATG GTCATATTAA GACTGTTGGC
8251  AATAAATGAG CTATAATTAT GTATGAAGCT GCTCTAAAAA TTATTTTTTT
8301  CTCTCACTTT ATTGCTGAGA CTGAGGCAAC TAAAATAGTT TTGATAATTG
8351  AAGAGGATAG ATGACAGAAT GAAAGAATGC ACATAAAGCC TTCCTCCAGT
8401  TTTACCTTTC CCCACTCCAA ATTCTGTGAA AGTGATATCA AGAGTCCAAA
8451  TACATTTTCC ACTTCAAATA GAAACTAGGT AGCATGGGTA ATGCAGTGTC
8501  AAATTCTTTC TCCTTAGAAG TATTTGAAAA ATCTTTTTTC ATAAATTATA
8551  CAGATCCGCT CAGAAGATAA CATAGCATTT GGAAATTATA AAATCTCTTA
8601  GAAACCTTAA ATTGAGATAT TTTTAAATAA CACAAATACT CATTTTTATT
8651  CAAGTAACTA ATATATCATC AACTAACACA TTGTCAGGAC TAGCTATATT
8701  TTTAGAGAGG TTTGTTAAAT GCAGTAAAGG TTTTTCATTT ATTCAAGAAA
8751  ACTTTAGAAA TTGAGGACAA TATTTTTTAT GTCTTTTAGT ATTTCTGTGT
8801  ACAGTAGAAT TATTTGAAAA AATAGGCCAG GCATGGTGGC TTCTGCCTGT
8851  AATCCCAGCA CTTTGGGAGG CCCAGCTGGG CAGATCATGA GGTCTGAGCA
8901  TTGAGACCAG CCTGACCAAC GTAGCGAAAC ACCATCTCTA GTAAAGATAC
8951  AAAAATTAGC TGGGCGTGGT GGCGTGTGCC TGTAATCCCA GTTACTCAGG
9001  AGGCTGAGGC AGGAGAATTG CTTGAACCCA GGAGGTGAGG TTGCAGTGGG
9051  CTGAGATCGC CCCATTGCAC TCCAGCCTGG GTGACAGAGC GAGAGTCTGT
9101  CTCCAAAAAA AAAAAAAAAA AAAAGCAGTC CCAGCTACTC AGGAGGTTGA
9151  GGTGGGAGGA CTGGTCGAGC CCAGGAGGTG AAGGTTGCAG TGAGCGATGA
9201  TCAGGCCACA GTACTCCAGC CTGGGTGACA GAGTGAAACT CTGTCTCAAA
9251  AAAAAAAAGA CTATCAAATA TGCAATGTTC ATTATCAGTT TATTATCAAA
9301  TTTGTAGAAA AATCTTTGTA TCCATTTATC CTAATATAAA TGTTATGTCT
9351  GACATATCAT AAGCACTTTA TATATTGGAT TTTATTATTA GCTTTTCCTT
9401  TAAAAAATAA TTGATGAAAT TTTGGACATT GGAAATTAGA TCCACATAGT
9451  TTAATTTCAT AATTCTTGAC ATGATGGAAG CCTTCAGATT TATTAAAACT
9501  ACCTGGTAGC TATAGAAAGA TACATAGCTA TTAAAAGGTA CATAATCTAG
9551  CTTAGAACTT TGAGGCTAGA AAGTATATCC CTTTATATAA GAGAGAGAAA
9601  AAGAATTCTA TCAAATGACC ATTCTGAAGA TAGAACATAT CTATCTGTAG
9651  ACAATACATT TCATGGCATT AGACATATAA AAGGTGTGTG CTATTTTTTT
```

FIGURE 3

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 9701  TAATGGTTAG AATTTTTGTA AAATCTGATT CTTAATATTC TTAGTTACTG
 9751  AATCAAATGG ATGGATTTGA TACTCTGCAT AGAGTTAAAA TGATCATGGC
 9801  TACAAACAGA CCAGATACAC TGGATCCTGC TTTGCTGCGT CCAGGAAGAT
 9851  TAGATAGAAA AATACGTGAG TTAAGATTCT TTACCTACTG TCCATTTCCC
 9901  TTTGTGCCCA TTTCTTTTTC CATACTTCAC TTCACCTTCC ACTGTATTTT
 9951  AAAAAAGATA AAACTGGACT ATAAAATAAT TTTTTATTTT CAGATATTGA
10001  TTTGCCAAAT GAACAAGCAA GATTAGACAT ACTGAAAATC CATGCAGGTC
10051  CCATTACAAA GCATGGTGAA ATAGGTAAGG AAGTCATCTA TTTTATATGT
10101  ATTTACATTT GGTAAATGAA GAAAAATACT TTTAGAAATT ACTGATAGTT
10151  TCCTAAATCT GGTTTTAAAT TCAGCAAATG TGGTGGTTTT AAATTCAGCA
10201  AATAGTTATT GAGCATCTAC TATAAGCTAG GAACCATTGT AAGTGTTTTG
10251  TAAGGGCTGA CAATATAGCA AGGAACAAAA CAGACAAATT TCTGCCATTA
10301  GAGAACTTAT ATTCTTGTTA GGAAAAAACA GATAAAGTTA GTAAAACAAA
10351  GTATAATAGA TGATGATAAG TGCTATGGAG AAAAATAAAG CAAGAAAGTG
10401  GGGGGCGGGC ATGGTGGCTC ACTCCTGTAA TCCTAATGGT TTTGGAGGCC
10451  GAGGCAGAAG GACCGCTTGA GGCCAGGAGT TTGAGGTTGC AGGGAGCTAT
10501  GATCATGTGA CTGCACTCCA GTTTGGCAAG ACGCTGTTTC AGGGGAAAAA
10551  AAAAGAAAAG GGGGATAGGA AATTAGGGAA GTGCCAGGAC CAGGCATGAG
10601  GATATGTTTT TAAATGACAG GGAGGATTAG CACAGGGAAG GCCTTACCAA
10651  GAAGGTAATT TATTTTTTAG AGACAGGGTC TCACTCTTGC CCAGGCTGGA
10701  GTGCAATGGT GTGATCCCAG CTCACTGCAA CTTCTGCCTC CCAAGTTCAA
10751  ATGATCCTCA CACCTCAGCC TCCTGATTAG CTGGGACTAC AGGCACACAC
10801  CACCAACCCT GGCTTGTTTT TTTGTAGGGA TGGGGTTTCA CCATGTTGCC
10851  CAGGCTGATC TTGAACTACT GGGCTCAAGC AATCTGCCCA CCTCGGCCAC
10901  CCAAAGTTCT GGGATAACAG GCGTGTGCCA CTGCACCCGG CCTGGTTGTT
10951  TGTTTGTTTG TTTTTTAAAT TGATTCCTGT TAAATGCTGA CAATAGGTCA
11001  GATAAAGAGT TCTCAGAGTA GACCTTTGGA TTTAACTATA TGGAGGTCAT
11051  TGGTAATCTT GTCAAAAGTA GCTTCTTGGG AGTGGTGGAG GTGAAAGCCT
11101  ATTTCAGATG GGTTTCAGAG AGATTGGGAG GAGAGGCATT GAGTTTAGAC
11151  ATTTCTTTTA AGAGTTCTAC AGAGGGGGCA GAAGAAGTAG AAGGGGAATG
11201  CCGATGAGGA GTTGGCAGAG TTTTCTATAA GATGGAAGAG TTTATGACCC
11251  CCCTGCCCTT TTTTTTTTTT TTTTAATAAT GCTACTGGGA ATGACCTAGG
11301  AGAAAGAGAA ATTGGCAATG TTCTTTCCTT GAAGAGGGAT TGGCCCTATA
11351  TATATGTGTA CTTTTATGAG ACTGGAGGAA AGGCAGAGTA CATAGATGCT
11401  TATGATGACA GGTTCTTAGA TAGTGCAGGA ACTTGTGGAA GTGTTTTTTT
11451  CTGAATGCTT CTGTTTTCTC AGTGAAGTAG AATGCACGTT CAGAATGAAG
11501  ATAGGGAAGT GTTCTTAGAG ATTTGAGGAC AAAGGAGAAG GTATAAAGTC
11551  ATTATCTATG GAAGTGAGGG ATTGGACTAG GGTGCAGGCC AGTAAAACAT
11601  GGCTTGTGAA CCAAATTCTG CCTGCCCTGT GTTTTTGGAA ACACACAAAG
11651  TTTTGTTGTA ACCCAAGCAT GCTCATTTAT CTGTTGTCTA TGGCTGCTTT
11701  CCTACTGGAA TAGCTGAGTT GAATAGTTAC AACAGAAACC ATATGGCTTG
11751  CAAAGCATAC AGTATTTACT CTCTGGCCCT TTACATAAAA AGTTTGCTGA
11801  CCTCCAGACT AGGGAAATCT AGTATAATTT CCAGGCAGCC TTAAAAACTC
11851  TTTAGAAGTT AATGGTCCAG AATAATGACA AATAGCTGAT TGTTGAATTT
11901  CACTATCTTC ATTGCCCCTG TTAGAGAGTT TTGAGCTGGA AAGACCGAAC
11951  TGAACAAAGG ATGTCAATGT ATAGGTTTCT TCCACAAATA CTGAGCTCTT
12001  GCTAGATGCC AGATACTGTG CTAGCCTTGG GAATTCTTGC TCTCAGGAAG
12051  CTTACAATGA ACTTAAACCT GATTAAAGAC AATTCATGAA TATATGTGTG
12101  ATTTCAAATA GAGAACGACA TGCCCTATAT TGCCTGACCA AACGGTGCAT
12151  CATCAAAGTT ATTCAAACTG TAGTAGCCTG TGCTGTCTTA CTTCTCTTCC
12201  TATTCTGTAT CAGATCCATT GTTGCTACCC CAATCCTATA GCTCTTTGAT
12251  TCATGTCTGT TATGTGGGTG GATGGAGAAC TCACTTTATT ACTGCTACCA
12301  TAGATCTGAT ACTTCACCAC TTGAATCTTG CACAGAAACC AGAGAAGCTA
12351  GCTAATGCAT GCTGTAGCAT TTAAAAATTC CATGTGATAC AATTATGTAT
12401  GATTACATTT CAGTTTTGCT ATACTTTATA TTTGGCTTGT ATGATTAAAG
12451  TAAACAAAGT AAATTCCATT GTTATAATTG GTTTTGAGTG TTATAGGTTT
12501  ATTCAAATCC AAGATTTGAT TACAGTTTTG ATAAGAGTCA CAGCTTAACA
12551  GGTATCTGGA GTTCACATGT GCATAGCTAT TTCACTGTAT AAAAATAGAT
12601  TAAGATATTT TGAGATTTTG GTGATATTTC CTGTTTTTAA AGTTTCAGGG
12651  GTGTGTCTAA TTCTTCTTGG TGCTGGTTTA TTTAACAGAA GTCTTAGTTT
12701  TTGGATATTA ATATTGTGGA AAGTTAACAG AGCTGATGTC TAGCTGATCA
12751  AACTCAAAGT AAGCTCTTCA GTTTAAATTT TCGATGTGGG CATAAATCAA
12801  GTAAAGGTCT AATTTTTAAA ACTAATTTCC AGTATTTTTT CTAAACAGAT
12851  TATGAAGCAA TTGTGAAGCT TTCGGATGGC TTTAATGGAG CAGATCTGAG
12901  AAATGTTTGT ACTGAAGCAG GTAAGGGTTT AAAGTACAGT TTTACTATTG
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FIGURE 3

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12951  ATTTTGATTT TTAAAATTTG CTGAAACTGT TTTGAGTTTA TCTGAAAGCG
13001  GAGCATAGAC TTTGCAAGGA TTTGGGTTCA TGCTGTTCTT TTAGGAATCG
13051  ATTCCAGGAA ATAGGAGAAG CAGGGCAAGT GAGATGGAAA GAGGGAAAGC
13101  TAATATGAGG GTGCACCATT GAGGTAGGTG CTGTAGGAAA GGGAGGTTAG
13151  ATCTCAGAGA AGCATACAGA ATGCCTTCCA GGATCACCCA GCTGAAAGTT
13201  GGGAGACTAG AACATTGATT TACCAGTACT CATCCCCCAT TGGATGAGAT
13251  TTGTCCTTGG TAGTGTTGAC TCCTTTGCAC TTCTACCTGC CTTAGGGCAG
13301  AATGTGGAAG GAGAGGCATG TAATAGAACA CTGGCCCCCT AAAGTAAGTC
13351  TGAGGTGCTA CAGAATTGCC TACCACACCT GTGGCTGGAA TTAGAATGGG
13401  CCAGCACCAG AGGTATCTGC TGCAAAATGA ATTGTGTATG TTGTCTAATA
13451  CTAGTCTGTG AGCAGTGTTT TGAAAGATTG ATTTATGAAT TATGTGATCA
13501  TGCCATTTGT GTAAAATGTA GTATTTAAAT ATAATTCTCT GTGGATTGTG
13551  TGATACTATT TTTTTCACTT CTACATGGTA TGTAAAAATT GTGTGATGCT
13601  ATTTTTATTT CCAGTACCAA GTAGCTTTAA TACCCTACCT AGAATCATTT
13651  AGTTTTTGTC TTCCATACAG AATCTTTAAA TAGAAAAAAT AAACTTCTAC
13701  AGTATAGTTA CTGACTTTAT AGGTTATAGA TTTTCTTAAG TATTAGAATA
13751  TGTGATTTCC TCTTGCTTTT CATATCATGT TTAGCCTTAG TAAATTCAAC
13801  ACAGTGTTTA AAGTGGCTGC TCAGGGAGGG CTTCTCAGTA CAGGTATCTT
13851  CATGGGTATT GGGTATGCTG TGAGTCAGTA TCTGCATCAG ATATGCAGGT
13901  CAGATACTTC TGTTCACGTC TAGAAATGCT GTCAATGCAA ATTAGGGTAA
13951  ATCATGCTCA CAGAGCGTTA TCAATAAACT AAACTATTTA GAGGTAAACT
14001  GTCATATAGC TTGAACAAGT TAGAGTAATT TATGACATTC TCTTTCCAAA
14051  ATGTAAACCA GACCAAATTA TTATCAGAAG ATTGCTTTGG TTAGATTGTA
14101  ATCCAAATGC AAGCTGTGCA GTGAACCTAA AGGCTGTTGC TATCAAAATA
14151  TACGCTTTTT TTCCTTACAT ATTCTTACAA ATTTACCTTT AGTTATTGCA
14201  AATGAGCTAT AACTTCTGTG TGGATTAAAA TTGTAGTTCT TTTTTAACTA
14251  GGTGGGACAT TCACATCTGG AAACATACTG AAATTTTTAT CTTCTTTTTA
14301  GACTTGAAGG CTTTTTTGTT AACATTTTTC GTAAGTTAAA ATACACTTGA
14351  TTCAACTACA GTTGCCCTTC CTGTTCAGGT CCTGACATTA TCTCTTTTGG
14401  ATTATAATAC ATCTCTATTT TATTTTTTCT TTTGAGACGG AGTCTCACTC
14451  TGGCCCAGGC TGGAGTGCAG TGGCATGATC ACTGCTCCCT GTAGCCCAGA
14501  CCTGATCATT TCTCCTTTAT CTCCCAGTAG CTGGGACTAT AGGCGTGCGC
14551  CACCACACCC AGCTAATTTT TGTATTTTTT GTAGAGACGG GTTTCACCAT
14601  GTTGTCCAGG CTGGTCTCAA ATTCCTGGGC CCGAGTAATC CACCCACCTG
14651  GGCCTCCCAA AATGCTGGGA TTACAGGCAC AAGCTACCAG GCCTGGCCAG
14701  GCATCTCTTG TGCAGATTTA CTTATTCACT AAAGTGATTT GGAAAATAGC
14751  CATGTGTGCA AGGTTTACAA AAATAACTTA CCTAGTTTCA CTGTAGCTTT
14801  CTAAACAAGT TTTGAAACTT TGTTATTTTT TAAAAATCAG TCATTTCCAT
14851  TCACCCGGTT TCTAGGACAA CATAGATTGT TTCCTTATGT AGAAATCTAG
14901  AAAGGAAGTA ATCCTTGAAA TCTTCTATAT TAACTCCCTC ATTTTATGTA
14951  AGTGAAAATT CAATACAGGC AGATCCTCAG TGGAAATTTT AGAATTCATT
15001  TAATTAGTAG ATAGCAATAA ACTTACCTGC TTTAGTTTAT CATGAGTTAG
15051  GATTATCTCA AAATCTGGGA CCCATATCCA TAACACAACT AATGTTTAAA
15101  AAACTGCATA CAAGGAAACT TTTACCCCTT TGTCAAATAC TGTTTGAGAA
15151  GGTACTTGTC AAAAAGTTGA AGGAAAAAAT TGAGTTGTGA TACTCAAATA
15201  TGAATCAAAT AAAAATACCA ATTTGTACAT AAATTAGGTA AATTTTAACA
15251  CATGAATAAT GACTCCGAGT TTTGCTAAAA CCCGCTGTTG GCTTTCTATA
15301  TGATTCCCTA TTCTCAACGT TTTTGATTAT TAACAAAGAA TGGCTATCAA
15351  ACTTACTCAA GATTTTTTTT CCCCCATAAA TGTGTGCCTT CCAGCAAATT
15401  GCTTCCTGTC AAGTTAAGTT ACGCTTAAAA TGTGTATGTG TTGGTAGTTT
15451  TGATTGCTTC GGTTTTTTAT GCTTGTTTTT ATTAAGAGCT ACAATCAGAT
15501  ACAGGGACCA TTTAAGCCTG ATTTTATTTT ATTTTATTTT TTTGAGACAG
15551  AGCCTCACTC TGTCACCCAG ACTGGAGTGC AGTGGTGCGA TCTTGGCTCA
15601  CTGCAACCTC TGCCTCCCGG GTTCAAGCGA TTCTCCTGCC TCAGCCTCCC
15651  AAGTAGCTGG GGTTACAGAT GCCCACTACT ACGCCCAGCT AATTTTTGTG
15701  TTTTTAGTAG AAACGGGGTT TTACCATGTT GGCTAGGCTG GTCTCGAACT
15751  CCCGACCCCA GGTAATCCGT CCACCTTGGC CTCCCAAAGT GTTGGGATTA
15801  CAGGTGTGAG CCACCGTGCC CAGCCTTGAA CCGGATGTTA AATATTCATA
15851  TAATGGTCAT ACCTGTTTTT GTTTTAGAAC ATAATCACAA CACCGCTATG
15901  GATTTTTTTT TTTTTTTTTT TTTTGAGATG GGGTCTCGCT CTGTTGCCAG
15951  GCTGGAGTGC AGTGCCACTA TCTCAGCTCA CTGCAACCTC CGCCTCCTGG
16001  GTTCAAGCCA TTCTCCTGCC TTAGCCTCCC GAGTAGCTGG GACTACAGGC
16051  GCGCGCCACC ATGCCCAGCT AATTTTTTTT TTTTTTGTA TTTTTAGTAG
16101  AGATGGGGTT TCACCGTGTT GGCCAGGATG GTCTTAATCT CTTGACATTG
16151  CAATCTGCCC ATCTTGGCCT CCTAAAGTGT TGGGATTACA GGCGTGAGCC
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FIGURE 3

16201 ACCGCACCCG GCCTGTGGAT TTTAATTGAA AAAAGATAGT GGTTTTTAGC
16251 AAATTACAAC TACTGGCTCA GAAGTAATAA ATCTAAGCTT CACATTTATT
16301 CCATAGAATT ATATTGTTTT TCTTATAATG AACATATAAT TCATATGTGA
16351 TATATAGCAG TCATGTTGTT TTATTCTCTA CAGGTATGTT CGCAATTCGT
16401 GCTGATCATG ATTTTGTAGT ACAGGAAGAC TTCATGAAAG CAGTCAGAAA
16451 AGTGGCTGAT TCTAAGAAGC TGGAGTCTAA ATTGGACTAC AAACCTGTGT
16501 AATTTACTGT AAGATTTTTG ATGGCTGCAT GACAGATGTT GGCTTATTGT
16551 AAAAATAAAG TTAAAGAAAA TAATGTATGT ATTGGCAATG ATGTCATTAA
16601 AAGTATATGA ATAAAAATAT GAGTAACATC ATAAAAATTA GTAATTCAAC
16651 TTTTAAGATA CAGAAGAAAT TTGTATGTTT GTTAAAGTTG CATTTATTGC
16701 AGCAAGTTAC AAAGGGAAAG TGTTGAAGCT TTTCATATTT GCTGCGTGAG
16751 CATTTTGTAA AATATTGAAA GTGGTTTGAG ATAGTGGTAT AAGAAAGCAT
16801 TTCTTATGAC TTATTTTGTA TCATTTGTTT TCCTCATCTA AAAAGTTGAA
16851 TAAAATCTGT TTGATTCAGT TCTCCTACAT ATATATTCTT GTCTTTTCTG
16901 AGTATATTTA CTGTGGTCCT TTAGGTTCTT TAGCAAGTAA ACTATTTGAT
16951 AACCCAGATG GATTGTGGAT TTTTGAATAT TATTTTAAAA TAGTACACAT
17001 ACTTAATGTT CATAAGATCA TCTTCTTAAA TAAAACATGG ATGTGTGGGT
17051 ATGTCTGTAC TCCTCCTTTC AGAAAGTGTT TACATATTCT TCATCTACTG
17101 TGATTAAGCT CATTGTTGGT TAATTGAAAA TATACATGCA CATCCATAAC
17151 TTTTTAAAGA GTATGATTCA ACGTAATATT TGCTAATATG TGACTGGGTT
17201 TTCTTGGTTT ATGTAAGACG ATAGGTCCCT GTTGAGGATG TGAAGGTCTG
17251 GACCCTCTTC CAGGAAAAAT TCTAACATAC AATTTTGCGT ATACTATAAT
17301 TTCAGGAAAT TTATTGTTTC CCAAGCTCAT CCAAGGATTC TTTAGGTATG
17351 TATGGATACC TGGCTAAGAG TGTATGATGT AGGGGATGTA GGAGTGTCAG
17401 AAATGTTCAA AACATGATTT CTGTTACCTA TACATGATTC TTATATCATC
17451 TGGCAATAAA AGCTATAACA AAGTACACAA AGGAATCATC ATTGGGCATC
17501 AATAATTATT AAAGATGCTG GTGAAAAGAA AAGACAACTT CAGTTTCATA
17551 AACACTAAAG AACCAAAAAT ACATGACCTA GCTAATTATA CAATAATTCT
17601 TCAAATTAAA AACTTCCTAG CAGGATATTA TGTGCCTTTT TATAATTTTT
17651 AGAAAGATGA ACAGTTAAAA TAGAAAATGG AGTGGTCAAG TTAGCCATCT
17701 CATACTCAAA ATTATTGTAC AGTTCTATTT CTATGTGTTG GCAGTGCATT
17751 TTATGTGACA AAAAGTAGAA TGTAGGGGGA GGTTTAAGTC AAATATCTAT
17801 GTGATCTTTT CACTTATAAT TTGCATTTAG TTAAGGAGTG ACTATCTTGC
17851 CTTTTACCTT TGTGCTGGCG GTGGTTTTTT AAAGAATCAA TTTGGTGTAC
17901 AAATCCTTTC TTTCTTTTTT TATTTTTGAT TTTTTTTGAG ATGGAGTTTC
17951 GCTCTTGTTG CCCAGGCTAT AGTGCCATTG CACTATCTCA GCTCATTGCA
18001 ACCTCCGCCT CCCGGATTTA AGCGGTTCTC CTGCCTCAGC CTTCTAAGTA
18051 GCTGCGATTA CTGGCATGCG CCACCACACC CAGCTAATTT TTGTATTTTT
18101 AGTAGAGACG GGGTTTTTCC ATGTTGGTCA GGCTGGTCTC AAACTCCCGA
18151 CCTCAGGTGA TCCACACGCC TCAGCCGCCC AAAGTGCTGG GATTACAGGC
18201 GTGAGCCTCC GCGCCCGGCC CAAATCTTTT CACCATGGGT TTACAGGCAT
18251 AACGCCACCA CACCCAGGGA ATTTTAAAAT TGTTTTTTAG AGAGGGGGGT
18301 CTTACTATTT TGCTCAGGCT GGCAAACTCC TTTTAAAAGA TATTGAAAGC
18351 CATCTGGTTT ATTATTTTTA TTTCAAAATA TAATAATGGA AGAAATTTTA
18401 CAGTATTATA TACAATTTAC TGAGTCAGCT ATCAGTTCCT TTTTCTGATT
18451 TTTTTCTAGT TGCCATTCTT GATATTTTCT AGGTAATCTA AACTGAGTTG
18501 TATTTTCAAG TACTCTTCAA ATACTTTAAA AAATTTTAAA TTGAGCCGTT
18551 TAATTCTTTG CTTAAAGGTG ATGGGTATTT TATTTTCTGT ATGGCACCAC
18601 GTGATTTTAA ATTGAACTCT TCATTTATTA GTCATTTGGT TATAAACTCA
18651 GCATAGATTG CGCAGAATTT TGAGAGGGGA GAAACTATAG CTTTCCTTTC
18701 GGATGCCACT GGTGGGTAGC CTGTTTTGCC TGTTTGTTCT TATGTTAAAG
18751 AAGGGCTCTA CGTCCTGTCT GGAAAGGGCG GAGCTGGCTC GGACCGCCCC
18801 ACTGCCTTTC CCAGGACCTT CACTCGTCCT GTCCCACCGC AGCCCCGCCT
18851 CCTCCACGCC GGGTGAGCTG TGGCCTAGCA GCATCCGAGG CTCCGCCCCC
18901 CCCACCCCCC AGCGTCTGCG CTCTAGCGAA GGGGCGGAGC AGGGCGGTGG
18951 CGCGCTGACA CCTGGCGGCG GCGGAGGGCG GGCAGAAGGC GAGCGTGGGC
19001 TGGGATTGGC TGAGGCGACG CGGGTGGAGG GGGCGGGAAG GAGGCGGGGA
19051 GACGGGTTGT CGGGCTGGTT CCTGTGCTGG ATCCTGGGCG GCCTGAGGGG
19101 TACGGAGACT CTGGGGGAGG GAGACGGCAG CGGCATGGCG GCCGGGTGTA
19151 AGACGCCCGA CCCTCCTCTT CCCTGTCTTC GCCGCCGCCG CTGCTGGAGT
19201 CACTGGGACC CTCTAGTCTG CGTGTGTTAG TTGTAATCCC GCCGCCCTCC
19251 TGTCAGCCCT CCGCTCCGCC GGCCCTCCTT CCTTCCGCCG CCGCAGCCAG
19301 CCCGAGGGTC GGCCGGCTGT GTAACACTCT CCCACCCCAC CCACCAGCCC
19351 GCGGGCCAGC ACCATGGAGG ACGTGAAGCT GGAGTTCCCT TCCCTTCCAC
19401 AGTGCAAGGA AGACGCCGAG GTGAGTCGCT CCCGTGGCTG CCACGCACAG

FIGURE 3

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19451  GCCTCTCCCT GTGGCTCCGG CCGAGGGGCG ACCCCAGTCC CCAACCGTCT
19501  TAGCCGCCAC CTGTACGGGC GCCCTGCCTC CTAAGGGCGT CCCGGGACCT
19551  CTGAAGCCGA GCGGTCGGCT CCAATCCCCA CTGAGTTGCT CGTCCTCTCC
19601  AGACCCCGCG GAGGGGCAGC GTCTGGTGTA CTTACATTTG AGAAGAGGAA
19651  AAGCAATCCC TTAGTCCCTA GGCTTGGCAT CCAGGACTGA CCTGGAGTAA
19701  GGTTCCTCTT TTATTGTCAA AGTAACAAGA GAGCGAAGTT GGTTTAGTCT
19751  CCTTTTGAGG AATATCTGTG GTGTAAACGA TTCACTTGTG GGACACATGG
19801  CCCCACATGT GAAATAGACT CGGCGCCTGA AGTTTGGAAG CGCGCCTTCG
19851  AAAAGTTTCC CAAAGTTTTT TGTTTGTTTT TGGACAAAGC TATGACCCGC
19901  ACAACAAAGT GTCTCAAAGC TAGCTCATCT TAATCTGAGA ACTCTTAATC
19951  AGAAATCTTG ACCTTTGGAG GAAAATTAAT ATTGAAAGTA AAATACTATA
20001  TACCTTTTCT CCTGGTTTCT AATTTGTGGC TATTTTTACT CCACCTTAGA
20051  TCCCTGCCTG CTGTTTCTAC TCGGATTTTT TTTCATCTGT TGCTAGTTTA
20101  ACATTTTACG GCATTGCAGA CTACTAAATT AGAATTTTCT GGAGGCTAAA
20151  TTAACAAGAC GAAGATACTC AGCTATACTT TAGTAGGATT AAGAAAGAAA
20201  ATCTAACATC GCTAGTTAAA AATACCTTTA AAGTAGTTGG GAAAAATAAA
20251  GCCCTATTTT TAGGAGACCA TTCAATTTAT TCCGAATATT TATTCTATTG
20301  AATATCTTCA TTGGAGGTTC ACTTTTTTTT TTTTTTTTTT TTTGAGACGG
20351  AGTCTTGCTC TGTCGCCAGG CTGGAGTGCA ATGTGGCGCG ATCTCGGCTC
20401  ACTGCAACCT CCGCCTTCCG GGTTCAAGCG ATTCTCCTGC CTCAGCCTCC
20451  TGAGTAGCTG GAACTACAGG CGCGCACCAC CACGCCCAGC TAATTTTTGT
20501  GTTTTTAGGG GAGACGGGTT TCACCATTTT GGCCAGGGTG GTCTCGATCT
20551  CCTGACCTTG TGATCCGCCC GACTCGGCCT CCCAAAGTGC TGAAATTGCA
20601  GGTATGAGCC ACCGCGCCCG GCCTAGGTTC ACATTTTTGT TTGGAGGGCT
20651  CTCTTGTGGT ATTGATGCTT GACAATTACA TTTGTTTTAA GAGTAGAGAC
20701  TTTGTTTGTG ACTATCACTG TTGCAAAATG TAGTGCAGTG GTGTGATCTC
20751  GGTTCACTGC AGTCTCGAAC TCCCATGCTC AAGCCATCCT TTCACCTCAG
20801  CCTCTGGAGT AGCTGGGACC ATGCCGGGCT AATTTTTCTT TTTTTTTTTT
20851  TTGTAGCGAT GGGTTTTTTC TCCAGGCTGG TCTCGAACTC TTGGCCTCAA
20901  GATCCTCCCG CCTTGTCCTC CGAAAGTGTT GGGATTACAG GTGTGAGCCA
20951  CTGCACCTGG CCCAAGAATA TACTCATGGT TTTTTTGTTT TTTTTTTTTT
21001  TTTGACACAG AGTTTCACTC TTGTTGCCCC AGGCTGGAGT GCAGTGGCGC
21051  TGTCTCAGCC CACCGCAGCC TCTGCCTCGG GTCCCGGTTC AAACAGTTCT
21101  CCTGCCTAAG CCTCCTGAGT AGCTGGGGAT TACAGGCGCG CACCGCCAGG
21151  CCCAGCTTTT TTTTTTTTTT TTTTTTGAGA CAGAGTCTCA CTCTGTCGCC
21201  CAGGCTGGAA TGATCTTGCA GTGGTGCGAT CTGGGCTCAC TGCAAGCTCT
21251  GCCTCCCGTG TTCACGCCAT TCTCCCGCCT CAGCCTCCCG AGTAGCTGGG
21301  ACTGCAGGCA CCCGCTACCA CACCGGGCTA ATTTTTTTGT ATTTTTAGTA
21351  GAGACGGGGT TTCACCATAT TGGCCAGGAT GGTCTCAAAC TCCTGACCTT
21401  GTGATCCGCC TGGCTTGGCC TCCCAAAGTG CAGGGATTAC AGGCGTGAGC
21451  TACCGCGCCC GGCCAATATA CTCTTAGAAA ACAGGAGGTC ATATTTAGGC
21501  TAGTTATAAA AATGAATTTA TACTTAACAT ACAATAATGT GAATGAAGAG
21551  TATGCTTTTA TTTATTTATT TATTTTTTTG AGACGGAGTT TCACTCTTGT
21601  TGCCCAGGCT GGAATGCAGT GGCGCGATCT CCGCTCACTG CAACCTCCGC
21651  CTCCCACGTT CAAAAGATTC TCCTGCCTCA GCCGCCTGAG TAGCTGGGAT
21701  TACAGGCGCC CGCCACCACT CCCGTCTAAT TTTTGTACTT TTAGTAGAGA
21751  CGGGGTTTCA CCATGTTGGC CCTGCTGGTC TGGAACGCCA GACCTCAAGT
21801  GATCCGCCTG CCTCGGCCTC CCAAAGTGCT GGGATTACAG GCTTGAGCCA
21851  CCGCGAAGGA GTATGCTTTC ATATCCTCAA AATGATTCAG TAATTTCAGC
21901  ACTTAACTGC AAGCAACCTT ACAAATAATG TAGAGGAGTC CCACATTCCA
21951  GGTGAAGAAA TTGTACCTTA CTGAAAATAA GTGATGTGCC AAATTAACAA
22001  CACAGTAGCA CAAGACACAG AAGGACCTCG GCCTCCTAAT TCATTGTTCT
22051  TTTTAATACA CTTCAATTCT TCCCTGCCCT AATCTTAAAA ATTCTAGTTT
22101  AAAATTTTCC CGGACTTTGC ATTTAATCTG TTACTGTGTA TATCATTATG
22151  TATGCCTTAT TCCTGCAAAA CTGATAAATT CTTGCTGGGA ATATATACCT
22201  GTCTTTTCTG TGTGGGACTT GAAAACACAC TCTTTTTTTT ATGCTACCAG
22251  ATGTGTGGGG GTTTTTCCAT ACCAAGCAGT TTTCCAGCAG GCATGAACTG
22301  AATGTCCCAT AATTCAATTC TGACACATAT GTACCTGAAG TTAGTCAGAT
22351  CCCACAGGTT AATGGGCTCA GTCCCGCAAG GCTGCCCCCA ACCTCAGATG
22401  GTAATCACAA GTAGTAGGTT GTCACCTATA CACTCCTGAC TGACTGTAAA
22451  TCAGGGTTCC CGTTACTCCC TCCTTGGTTC AGTTAACTTG CTAGAGTGAC
22501  TTACAGGACT CAGGGAAGTA CATTTACGGG TTTATTATAA AGGATACTAC
22551  AAAAGATCAG TGAACAGCCA GTAGGAAGAG ATGAATAGGG CAAGGTATGG
22601  GGGAAGGGGC ACACCACCAT CCCAGTGTCA CCAGTAGAGT CATGATTGCA
22651  AGCTGTCCAG GTTCTTGGCG TTTTGAACAA AGAATTGGAC AAAACTCCAA
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FIGURE 3

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22701  GCAAAGAAAG AATGAAGCAA CAAAAGAACA AAAGCAGGGA TTTATTGAAA
22751  ACAAAAGTAC ACTCCACAGT GTGGGAGCTG CCCTAGCAGC ACTCCCCCCC
22801  GACCCCCGCT GCTTTACCGA ATCTTCTTGG GTCCAAATAC CCCCTAGAAG
22851  TTTCCCATTG GCCATTCCAT GCTCACCTCA TGTAAATGAA GAGGTGGCTT
22901  GCAATTGGTC TGATTGGTTG CCAGACCCAC CCCCACATCA GTCCGCTTGG
22951  TTGTGGACAG CGACCATTCA GTGGCTAGAG TGAAGTTACA AAGTTGCAAA
23001  CGAAGATTCC ACCCGCAGTC AGTCTGATTT GTTGAGGACA GCCAATTTCC
23051  CGTCTACTGT GCAGAAAAGG TAGGTGGTTT GCAACGGGAG TAGCCTCTGG
23101  TCCTTTTGTT ACTTAGGCGT GGAAAGTTAG GGTTTTCCCT TCAAGTTAGT
23151  TCTGGGAAGT CGGGGTGAAA CAGCCTTAGA TTCCCTGCCT CCAGACCCTA
23201  TTCACCTGCC TCACTAGCAC CTCCAGTGTT TTCATCCAGA AGCTCAACAA
23251  ATCTTATTCA ACGGTTTTTA TAGAACTTCA TCTCCATCCC CTCCCATAGA
23301  GGTGTGTGTG TGTGTGAGGC TGAGAGTTCA ACCCTCTTGT CACATGGTCT
23351  TTCTGGTGAC TGGCCCCACC CTAAATCACT TCATTAGCAT AATCAGGTTT
23401  GATCAAAAAT AGTGGCTCAT AAATAACCAA AGACACTCCT ATTAGAAAAT
23451  TCCAAGAGTT TTAGGAGGAC TGTGACAGGA ACTGGAGAGA AAGACCATGT
23501  ATTTCATATT ATATCACAGG GACAGAGGTA ATGGTTAAAG CTAGTGGATA
23551  ATGATGCAAG TATTGTCTGC TGAAAGCCAA TTCGTTCCGT ATTTCTTAAT
23601  ATTGCATGTT TGGTATCTTT TGGTTGCAAG CAACAAAAAC GAATTTAAGA
23651  AAAAGAAGAA GTAATTAAAT CCGGCCGGGC GCGGTGGCTC ACGCCTGTAA
23701  TCCCAGCACT GTGGGAGGCC GAGGCGGACG GATCACGAGG TCAGGAGATC
23751  AAGACCATCC TGGCTAACAC GGTAAAACCC CGTCTCTACT TAAAAAAAAA
23801  TTAGCTAGGT ATGGTGGCGG GCGCCTGTAG TCCCAGCTAC TTGGGAGGCT
23851  GAGGCAGGAG AATGGCATGA ACCCGGGAGG CGGAGCTTGC AGTGAGCCGA
23901  GATCTAGCCA CTGCACTCCA GCCTGGGAGA CAGAGCGAGA CTCCATCTCA
23951  AAAAAAAAAA AAGTAATTAA ATCCAGAAGG GTAGTGGTGC AGCTAGTTTC
24001  AAGGATTTGA CCAAACCCAG GTATTATAAA GCATCAGAAC TGCCTTTGTC
24051  TCTCATGAGT TCTTATCTCT ACTTTCTCTC AGAGTCTCTG CTTTCTCTCT
24101  GGCTTCTCCA AGATGTGAAG CTTGGCCATC TGGGGTCACA CCTTTATGAG
24151  CTTGGTTATT GAGGAATAAA ACTGAACACT TCCAGCTTCT GTGTTTGAAA
24201  TCTAGAGGAA TTGCCCAATT TAATTCATGT TCCCACACTT TGGATCAGTC
24251  ACTGTAGCCA GGAAAGGGCA GATACAATGA GGGGCCCCAT CTAGGTCATA
24301  TCCCTAATTC CTTGGCTAGA GGAGTGAAGT TTATTGTTGG TAGCCCTCCC
24351  ACCAAAACCA TAGGAACATT TCCACAGGTA GAGGGTACTT TCTGGGCTGA
24401  TAAAACTATA CATAGGGGCC ACATAAATAA ACTATTAAAT AGGAGCATAT
24451  AGTTATTCAT AATAAACTGA CTAATAAGCA CTGTTAATTT TCTAATCTCC
24501  AGTGAGATAA TGTAAAGTGT CAAATGGTCT TAAGTAGTTA GAGTGATCAG
24551  CCAGCATTGT TTCTTTGACA CAGGGAGCAC TACCTGGAAA TCCAAATTAC
24601  AGACCAAATT TAATAAAAAC GGAATTCAAG CAGAGAGTTC AGGGAATGCT
24651  TTTAATGTTA ATGTGATCAA GCTATGATAG GTTGATGATT CTGTCACCTC
24701  TACAAGAATA TTACTTTCAC GTTTCTTGAA ATATTGGTAT TCTTTGTATA
24751  GGACAGTGCT AACAAAAATT TAGATCAGTC AGTTTGTGAA AAGATTGTTA
24801  CTTTTTTTGT TTAAAACTTT TTCATGAATT TCCATTGTTT TGAAGATGAA
24851  ATTTAAACCC TTGACATTAT TTCCAGGGTC CTGTATGGTC TGACATCTGC
24901  ATACCTCTCT AACCTCATTA TGAGCTACTC TTCTTGCTCC TTTCTCTGTA
24951  AGCCCTAGCC ATATTTATCT TCTCTCAGTT CCTGGAATGC TTTAATTTCC
25001  ACCCCCCGCC TTCAGAGCCT TTATGTTTGC TATTTTCCCC TGCCTTGGCT
25051  GCCAGCACCT TCCTTACCCT CACCTAATTA ACTGCTTACC CTTGGGTTAG
25101  ATCCCACTTT AGGCAACATT TCTTCAGAGA AGCTTTTCCT GTTTGCCAGT
25151  TTCTCTAACT CCTTTCCTCA TCCTCTAGAC TGGTTCAATT CCCCAGCTAC
25201  TATGGCACTT GGTACTTTAA TACTTACCTT TGTAACATTT AACAATTTTT
25251  GGTCATTGTC TATTTTCCAT TTAGACTGAA CCTTTCATAA GAGAGCTTAG
25301  ATATTAGGAA GAAGGAGTAG CTGATAGTAC CAATTTTTAA GCAAATTGGT
25351  TGTAGCTGGG GCTATTGGTT TTATAATTTA AAAGTTAATG TTTTATCTTC
25401  TCTTCTGACA GAAAGTGAAA TATTTATTTC CATTGCAGTT TAGCAACTTT
25451  CCATGTTTCC CTTTCCATTT TTCTTGTGAA TCCCGTAGTA CAGGATCAAA
25501  GATAGGAATT ATTTAACATA CATGGCTGAG GATTCCTTTT CTAGCTCCTT
25551  TATTTAGAAT GGTGCTTTTT AACCCTTACT CTAGAGTAAG GAATTTTTTA
25601  AAAATACTGA TGCCTGGACC CTACCAGCAC CTATTGTAGT TTAATTTATC
25651  TGAATGAAGC TAGATGATTC TAATGTTCAG TCAGGTTTAA AAATTGCTGG
25701  TTTAGAAAAT ATCTTGAGTA CTCTTCTGCC CCTCCAGTCC CTGCCCACCT
25751  TCTCTTTTTA TTTGAGTGAA.ACATTTTCTT TTCTCCTTTG ATTTAAGCAA
25801  AGCTCAAGCT TGGTGTGGGA ATGAAAGGAA AAGGACTTTG GAGGGATTTA
25851  CCTATTTTTT CTAGGAGAGA AAGTGCAATA CTAACTTTTC TGTTTTGTGG
25901  AATGTCCCAG TGCAAGTCTA GTATTCTGAT GTTTTTTTTC TTCCCCAAAC
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FIGURE 3

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25951  TGTTGCCCCC CACCTCCAGC CTATGTACAA TTTGTGTTTT ATTTTAGTAT
26001  TGTGTATATA GGATTCAGCA CTATCCTCAA ATGTATGAAC ATATCCCCTG
26051  TGGATAAGGG GGGACTACTG TATTTGTAAA AGTTCATATT TCATATTTCA
26101  ATGCATATAA GAATTATTTT ATCTAATGGT TACAGTCTAT ATCCTTCATT
26151  GATGTGTTTA TTTGAGGGTC TTTGAACATT TTTGTAACTT TTCTCTATCC
26201  AAATGCAGTT TTATAGATCA TTTTTATGGA AAGGAAGGAG ATAATTCGGA
26251  AGGATGTTTT AACATGTGGT ACTTTCTACC TCATGTTGAT CGAAAGATTT
26301  TCACTTGTGA ATTAATTTGT CTCAGAATCA TGGTGTTTCA CAATAGAGGG
26351  TTATTTTGGT TTATCTGGCT TGCCTTGGTT TGGTTAATGT GGTTGAACTG
26401  CTTGGCTACT CATAAAGTTT GGGAAATTGA TTTCTACTAA TTAATTACAA
26451  TAGTAACTTA AAATAGATCA TTGCTGGTGA TATGGAGATG CCTCCATTAA
26501  TACCACGGTT TCTAAAATGA TAGATTTCAG GAGTAGTGTG AGCAGGCTGA
26551  GATTAAGAAT TAAGTGTGAT AGTGGCAAGA CTTGGTTATT AGACGTGTGT
26601  TCAGACGGAT GTGTGGTAGA AGAAGACTAT GAGCATTCAG ACTTAAAATC
26651  TTGGTTAGTA AGATCCATAG ACAGGCAGGG TTTTTTTGTT TGTTTGTTTG
26701  TTTTAACAGG TTGGAGTGCA GTGGCAGGAT CTCAACTCAC TGCAAGCTCC
26751  GCCTCCCGGG TTCACGCCAT TCTCCTGCCT CAGCCTCCCG AGTAGCTGGG
26801  ACTACAGGCG CCCGCCACCA TGCCCGGCTA ATTTTTTGTA TTTTTGGTAG
26851  AGACGGGGTG TCAACCATGT TAGCCAGGAT GGTCTCGATC TCCTGACCCT
26901  GTGATCCACC CTCCTTGGCC TCCCAAAGTG CTGGGATTAC AGGCGTGAGC
26951  CACTGTGCCC GGCCAACAGG CAGGTTTAAG GTTTGTTCTG TAGGTGGTAA
27001  TCTGGGTTAG GGCAGCAAAG AAGGTGGATT CTGAGATCAG CATCTGATGA
27051  TAACACCAGG AATAGTTCCA AATGAACTTT TCTGTGAGAG AAAGCTTTCT
27101  AGGTTTCAAA GGATCCATAC CTATTGCAGT AATTACTAAT GTTCTCTGAA
27151  GAAGGCTTCT TATCTGTCCT GTGACTAGGA ATAATTTTTC ATTCCCTCCT
27201  ACTATACAAC TTGCTTTTCC CTCTTATAAT ATCTTCCATA TATATATATA
27251  TCTCAAGAGA GTCTTTCATG TTGTATTACA TATAACCTTA TGGAAAGCTC
27301  AAAAGTTCTT TGAAGCCTCT TGTTTTGCTA AAAGGTTCAG GTAAATTTTG
27351  CATTCTATCC CATATGTGCC TGTTTGTTTT AATATAAAAA TTGTTTAAAT
27401  TAGTAACCAG TGAAAATACT GTTTCTCCCT AAAGAATTTT TTTGATAAAA
27451  TTGATACTTC AGTGGCTTTG AGTGTCTTTT GGCATATTGC CAAATGAAGG
27501  TGTTGAGGAA ATGCCACTCC AAAATATGAC ACCTTGATAT ATTGATTACT
27551  TTAAGTTGGA AACACTTGCA AAGTAGCAAA TGCAAAGAAA CACTTTCTCT
27601  GAACTCCTGT TACCTACCTA AGGACAGATC CTCCAAAAGA AGCTCAATTT
27651  GCTCCTAGGG AGTTTGATCA ACCAGGGAAG ATTGTCTCTT ATCACTGGAG
27701  AGGAGAGTAA AAGTCAGCAC CACACCCAGA CAAACTGACA CAAAGTATCA
27751  TCTATTATTA TTCTAAGGGC CCATTTATCT TTCTCCAGAA TTGTTCTTCT
27801  AAATTGCCTG TATACCTCTA CCCCCATGCT ATATAAAGGG TATATAAACT
27851  CCTAAATATC ACTTTTTTTT TTTTTGTATA CACGTTTCTT TCCTGTGATA
27901  CCCCCATGCA CATAATGAAT CTGTATACCT TTTCTCCGTT TAGTTTATTT
27951  CATAGACTGG TTTGAAATAT CACGGATTTT GTTTGTTTTT GGTATACACT
28001  TTTTAAAAAT ATCACTTTTT TTTTTTTGGT ATACACTTTT CTTTCCTGTG
28051  ATACTCCCAT ACACATAATA AATTTGTATA CATTTTCTCC ATTTAGTTTA
28101  TTTCATAGAC TGTTATCGAA TCCTGATGGT AGAGGGAAAG TCTTCCTTGC
28151  CTTACACAAG TATTTCCCAG AATATATTTA CACCATTCCT TGATATGTGT
28201  TGCCCTGTTT TTTTTTCTTT AATTACACAA AATTTAGTGA TTTCACTTTA
28251  GATAAATTCA AAAGTACGCA TTTCTTTAAT TGATTTTCTT CTTTATCACA
28301  GCTCTGACAA GTTGCTTCAG GAAGATAAGG CTGGCTGTTA GACTACTTGA
28351  GAATCTTTTA AAAAGAAAAA AGTCAATAAC ATTTAGTGCA GTAGATCTCT
28401  GAAATGCATC TATTTTGTGC TTATTCTGTG TCAGGCACTG TGCTTATCAT
28451  TAGGGGTACC ATGACTAAAA AGAGTATTTG GCCTAAAGTC TTTAAAAACT
28501  GTTTTCTTTT TCCTTTCTTT CTTTTTTTTT TTTTTTTTTT TTTCGTTGAG
28551  ATAGGGTCTG TCTCTGTTGC CCAGGCTGGA GTGCAATGGC ACCATGATGA
28601  CTCACTGCAG CCTCGACCTC CCAAGCCCGA GTGATCTTCC TGCCTCAGCC
28651  TCCCAAGTAG CTAGGACCTC AGTCATGCAC CACCACCGCA CCTGGCTAAT
28701  TTTTTAATTT TTGTAGAGAT GAGGTCTCCC TATATTGCCC AGGCTGGTCT
28751  TGAACTCGGG CTCAAGCTAT CCTCCTGCCC CAGCCTTCCA AAGGGCTGGG
28801  ATTGCAGGTG TGAGCTACCA TACCTGGCTA AAAAACTCAT ATATAAAAAG
28851  ATTACCATAA CACATTGGTA AGTTAAAGAA TCTAGGCTGG GCGCGGTGGC
28901  TCATGCCTGT AATCCCAGCA CTTTGAGAGG CCGAGGCAGG TGGATCATGA
28951  GGTCAGGAGT TCAAGACCAA CCTGGCCAAG ATGGTGAAAC CCCATCTCTA
29001  CTAAAAATAC AAAAATTAGC CAGGTTTGGT GGTGGGCGCT TGTAATCCCA
29051  GCTACTCAGG AGGCTGAGGC AGATAATTGC TTGAACCTGG GAAGCGGAGG
29101  TTGCAGTGAG CTGAGATCGT GCCACTGCAT TGCACTCCAG CCTAGGCGAC
29151  AGAGCGAGAC TCCGTCTCAA AAAGAAAAAA AAAGTATCTA GTAAACAATT
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FIGURE 3

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29201  ACATTTCCCT CATTGCTGGC TTAGAAATTA CATGCTTTAT TTCTATTCTG
29251  TTAATATCCA TAAATTAGTC ATTATTTTAT GCAGCCAATA TTTGTTTAAT
29301  TGTAACTGTA TGTTTGCCGT AAAGTTCATT CTTACATTGA AAGACTGTAT
29351  AGTATATTGA TTCAGAGAAT GAACTCTGGG TTCAGACTAT CTGGATCCAA
29401  AATCAAGTTA CTTAGGTTCT CTATGACTAA AATAGACAGT GATAGTATCC
29451  CTTCTTCAAA GAACATTTTA ACTTTTTTTC TTTAAAGATA TTTTTCCGAG
29501  CATATATTCT TAATTAACAG TTGTTTTTGT CCTGCCACTA TGAATGAATT
29551  ATTTGTGTCC TCTGGCTTCT GTTCATGCAA TTGAGAAGTC AGTGTCCATC
29601  TGATTGTCCT TCCTTTGTGT GTAATCTGTC TTTTGTCTAG TTGATCTTTT
29651  TTAATAAAGG TAAAATTTAT ATAGTGTAAT GTACAAATAG TAAGTGTGCA
29701  GTTCATTGAG TTTTGATGAA CATACACTAA TCCACCCCAT CAAGATACAA
29751  GAACATTCTA TTAGCATAGA AGGTTACATC TATTTCCAGG CATTTCCTCT
29801  CCCATTCCAC AATAGGAAAC CAGATTTCTA TCAACATAGA TTAGTTTTCC
29851  TTGCTCTTGA ACTTGATACA AATGGAATCA TGCAAATGGA CTCTTTTGTG
29901  TGTGGCTTTC TTCACTGAGC ATAATGTCAA TGAAATTCAT CCATGTTGTT
29951  GTGTTTATGA GTACTTCGTA GACTTTTATC CCTGAGTACT ACTATTCCTT
30001  TGTATGAAGA GACCATAGAC ATTTGAGTTC TTTGAGACTA CAATAAATAA
30051  AGCTGCTATA AATATTCATG TATAAGTCTT TGTGTGGATA TATGTTTTTA
30101  TATATATATA TATATTTTTT TTTTTTTTGG TAAAGCCTAG GAGTGGAATG
30151  GCTAGATATT ATAATAGGGT AGGTGTATGT TTACCATTTC ATTTTACATT
30201  CCCACCAGCA ATGTGTGAGA GTCCCAGTTG CTCCACATCA TCACCAGCAT
30251  TTGGTGTTGT CAATTTTTTT AACTTTAACC ATTCTAATGG TAGGTAATGA
30301  TATCTTTTGA TTTTACTTTT GAGTTTCGTG TGTGTGTGTA TGAGAGATGG
30351  AGTCTCACTC TGTCACCCAG GCTGGAGTGC AGTGGTGCAA TCTCGGCTCA
30401  CTGCAGCTTC CACCTCCCAG ATTCAAGCAA CTCTCCTGCC TCAGCCTCCC
30451  GGGTAGCTGG GACTACAGGC GTGCCACCTC CATGCCTGGC TAATTTTTAT
30501  ATTTTTAGTA GAGACAGGGT TTCACCATGT TGCCCAAGCT GGTAAACTTC
30551  TGAGCTCAAG TGATCCGCCT ACCTCAGTCT CCCAAAGTAC TTGGTAATTT
30601  ACAGGTGTAA GCCACCGCAC CTGGCCTATT CACTGATTTT TAATTTCAAT
30651  TATACTTCTT ATTTCTACAT ATTCTGTGTT TTTAAAAATC AATTTCTTAG
30701  TCTGGTCATA TTTTGATACT CTAATTTCTT TAAATTTTTT ATATTTTTCG
30751  TTATTGCTTA TAATATCTGC AGTTTTGTAA GTGTAACTCA GTTGTTTCTG
30801  CTTCCTGTGG TGGCTCATTT CCTGTTTTTA AATTAGTTTT TGATTGTGAG
30851  CTTGTTGGGA CTTTATCTGT GTGAATTATT TCTGATCTAG GTTTAAGGTG
30901  TGTTTTTCTA GAGAATATGC ATTTGCTTCT TCCAGGAATC CAGGGATGCA
30951  ATCTACCCAG GACCACTTAC ATTAAATTCT CACTTGGCCT CACAAAAGTA
31001  ACTGAATTCT AACCCCAAAC TTGAGTGGAT GCCAGATTGT GGTTAGGAAG
31051  ACCCCACTCC ACCACTACCA ATACCTACCC AGAGCCAAAG CTAGGAAGGA
31101  CAAGAGTACT CACTTCTGTG GGATGAGTTG AGTTTTTGTT TTTCTTTCTT
31151  TCCCTAGTTT ATCTTTCACT GAGGATGTTG CCTTTGGGAG TTCTAGCTTT
31201  TTGGTCTTGA TCTGAGTTCG ACTTTGAGCA GATCATAGAC TTTGTCTTAT
31251  GTTTACAAGT ACGTTTCCAC TTAAAATAAG GCCGTAGTGA AGATGTAGAA
31301  CAACTAGAAG TCCCATACAT TGCTGGTGGG AGTGTACAGT GGTTTTACAA
31351  AACTTTTGGC AGTATCTAGT AAAGCCAAAC ATAGGCCTAC CCTGTGTCAA
31401  AAGACAAAAT TACAACAAAT TTAGCTTAAA AATCTAACTC ACTTTTATTA
31451  GTGGTTCATG AATCAGGCAG TGTGTCATCA AAAGATTTAG AAAAGGCATT
31501  TCAGTGTGCT GAGCAGAGGA AGTTGAATTT ATAGGCAAAA TCTAGCTAAA
31551  TAAAGCAGAA ATGAAACAAA AAGTGGATTG GTCATTTCAA AGTTAGTTTC
31601  TTTATAGTAT TAAAACACAG GGGACTTCCT TATGCTGGCT CAGGATAACT
31651  GGCCTCCTTC TGATTGATTG CTATGAATCT TTTGATTTTT TTTTTTTTTT
31701  TGAGATGGAG TTTCACTGAT GTTGCCTAGG CCTGGAGTGC AATGCCACGA
31751  TCTCATCTCA CTGCAACCTC CGCTTCCAGG CATCAAGGGA TCCTCCTGCC
31801  TCACCCTCCC ACGCAGCTGG GATTACAGGC TCCCTCCACC ATGCCTGGCT
31851  AGTTTTTGTA TCTTTAATCT AGAAGGACCC CCACCCTGCA GCCCAGGCGA
31901  CAGACTGATA CCCCACCTAA AGAGATCCAC CCGCCTCATC CTCCCAATTT
31951  GCCAGGGGGC AGACTGCATT CCACCGGTCC CTGATTTGGG TGCTTAAAAC
32001  TCAGAATTTT CTTGGGGATT TTGGTCTCCG ACGTTATCGG GGAAAACTGT
32051  TTTTAACCTT TTATTTTGAA ACAATTTTAG GATCTTTGAA AAGTTGCAAA
32101  AATCCTCCAT GGAATTCCAT TTACCCCTTC CCCCAGTTTT TTCTTAGNNN
32151  NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNGGC
32201  TCCCGCCCCA TGCCTGGCTA ATTTTTGTAT TTTTAGTAGA GATGGAGTTT
32251  CACCATGTTG GCCAGGCTGG TCTCAAATTC CTAACCTCAG GTGATCCACC
32301  CGCCTCAGCC TCCCAAAGTG CTGGGATTAC AGGTGTGAGC CACCGCGCCC
32351  GGCTTTTTGA TTTTTTTAAA CTGTCATTAC TCGGGGTTTA TAGTCTACTA
32401  CTATATTGCT GAGAACAGTT TTCAAGATTA AAAATAAAAA TGTTTTCTGT
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FIGURE 3

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32451  TTCTCTTAGT TAAAAAAAAA AACCTGTCTC TCATTGTAGG ATTATTATTC
32501  TCTCTTTTCA TTATAGATGT ATACTATTTC TACCTTCTGT GTTAAAAATA
32551  CTTTTCTGGG CCGGGGGCAG TAGCTCACTC CCGAAATCCC AGCACTTTGG
32601  GAGGCCGAGG CGGGCAGATC ACGAGGTCAG GAGATCAAGA CCATCTTGGC
32651  TAACACGGTG AAACCCCGTC TCTACTAAAA GCACACAAAA AAATTATGGC
32701  GTGGTGGTGG GTGCCTGTAG TCCCAGCTAC TCGGGAGGCT GAGGCAGGAG
32751  AATGGTGTGA ACCCGGGAGA CGGAGCTTGC ATTGAGCCGA GATCGCGCCA
32801  CTGCACTCCA ACCTGGATGA CAGTGTAAGA CTCGGTCTCA AAAAATAAAA
32851  AAATAAAAAA AATACTTTTC TGACTTAGAG AATCTGGGTG AAGGGTAAAT
32901  GGAATTCCTT GTACTATTTT TGCAACTTTT CTATAATCCT AAAATTGTTT
32951  CAAAATAAAA GGTTAAAAAA ATATTTTCCA GACTACTTCA GAAACCTAAT
33001  TACTAATAAT AATTCTGAGT TTTAAGCAAC CAACTTAGAA ACTTTTGGAA
33051  TGCAGTCAAC CCACTGACAA ATGAGGACTA TCTGTACTAT AGTATTTTTT
33101  TAGACGGGGT CTCAGTCTGT CACCCTAGCT GGAGTGGTGG GGTGATCTCA
33151  GCTCATTGCA ACCTCTGCCT CCCAGGCTCA AGCGATCTTC CCACCTCAGC
33201  CTCCTGTGTA GATGGGATTA CAGGCAGGCT CCACCATGCC CAACGAATTT
33251  TTTTGTATTT TTAGTAGAGA AGGGGTTTCA CCCTGTTTCC CAGGCTGGTC
33301  TCAAACTCCT GAGCTCAAGC AATCTGCCTG CCTCGGCATC CCAAAGTGCT
33351  GGGATTACAG ACATGAGCCA CAGAGCCTGG CCTTTTAGTC TATTTCGATT
33401  CTTCATTTCA ATTCACTATA CTTTTTTTCT AAGTTTTAAA ATATTTTTTA
33451  TCTTTTACCA TTGACATTTT GTGTTGTTTT ACAGCTTCTT TATATTGGTC
33501  TGCATTCCAA AGACAAAATG AAGTCTCTTA TGTTTTGTGA TATGTGTTAA
33551  AATAATTGAA CTAGACAAGA ATGTTAGGCC CAAGTGAGAT GAAGGAAAGG
33601  CTCTTTGATA AGCATTTGGC ATTTTAGATC AGAGATGGCA AGTACGTATG
33651  ACATAGCATT CTTCTTTTAT ACATTTCAGA TATTATTTGT TGATCAGACA
33701  CTCTTCTTCC TGTCTTGGAC CACACAGTGT TTTAGGTATC TGCTGTCAGT
33751  TGATCAGAGT TGGCATGAGA AACAAAAAAA ATCTATTGGC ATCTCTGACT
33801  TAGAAGATCA GTTTTGGGAG AATCTTCTGG AATATCTATT CTATTCTTAA
33851  GTTTAATGAG TAATTTCATC CATTTTATGA AGTAACATAA CAATTCTGGA
33901  AGCCTAGTTA TTTAAAGAAT GCTTTAAGCT TTGTTTCTTG TCACTTCAAT
33951  TTTCAGATGT TTGTGAAACC AAGTCTGCTA TTTTAATAAA ATGTTCTTAA
34001  AGTATAATGT AACTTTAAAA AATCTACATA CTTGTGTGTC ACATCTTTAG
34051  CCTTTAATTG GGTGACTTTT TAAATGTTAT CTACTTTTAT TCTTATGTTT
34101  TCCTTCCCAG GAGTGGACCT ACCCTATGAG ACGAGAGATG CAGGTATGGC
34151  AACCTTTTCT TTGTTCAAAC CAACCCATGT TATTATCATA ATAAGAACCT
34201  TAGTTTATAG GATTTGAGAC CTGCTGATTT CATGATCTGT AGGTTCATCA
34251  TTATGTATTT TAAATAATTA TTTTAAATAT TTAAGGTTAA TCTTGGATCT
34301  TAAAACGATG GGAAATTAGA AAGAGGAACG TAGTAATAGG TGTATGTGCT
34351  TAATGAGTCA CTTTCTCTTG GTTTTTTTTT TGTTTTTTTT TTTTTGAAAC
34401  AGAGTTTCGC TCTTGTTGCC CAGGCTAGAG TGCAATGGCA CGATCTCGGC
34451  TCACCGCAAC GTCCACCTCC CGGGTTCAAG TGATTCTCCT GCCTCAGCCT
34501  CCCGAGTAGC TGGGATTACA GGCATGCGCC ACCACACCCA GCTAATTTTG
34551  TATTTTTAGT AGAGACAGGG TTTCTCCTTG TTCAGGCTGG TCTCACACTC
34601  CTGACCTCAG GTGATCCAGT GACCTCAGGT GATCCACCCA CCTTGGCCTC
34651  CCAAAGTGCT GGGATTACAG GCATGAGCCA CCGTGCCTGG CCAATGAGTC
34701  ACTTTCTTTT TCCTCACGTG AAAAATTGGA TACTTTCTTT GTATTCCTTT
34751  TGAAAGCAGT TTGCTTTCTC TGTTTGTCTA GATAAGTTAG GGAGAGTTGT
34801  CTGTACAACA AATAAGCATT GTTCATTTTG TGTCCGATTT TTAATCAACT
34851  TCCACAATTA AGTCTTCTAG AAGATCAAAT TGAATACTTT CAGTTTGGAA
34901  TGAATTAAAC GATAGCTAAC CCTCATAGCA GTTCATTTTC TTTTGCATTT
34951  CATACCATTT ACCGTCAAGT CTGTTTGCCC CAGGATTAAG CAGTATCTTG
35001  TTCCTGGGAA TCCCATGACT TCTAAAAATC TGTTACTTTT CTCTCTTAAT
35051  GAAAGTTCAC TTTGAAAAAA TAGGTGAGTA CCTATGAGGC ATTTTACTTG
35101  GTGTTAGGAG GAATGCAAAG ATGACTAAAT GTAATTTCTG CCCACAAAAG
35151  CCTGGTGGAA GAAATCAGTT TTATATACAA ATAATTATGA CTTATAGAAC
35201  TGAACTATAA AGTTACTGTT AGTATCTAGG GTATGATATA TCCAGACTGA
35251  AAGCTTTCTG TATTGAATTT ACATAAAATA AATTTGAATT CAACATCTGG
35301  AAGGTACATA CTTGTTGAAA TTTTGTCAAC TGGCAAATAT TTGAATTTGG
35351  AATTTTTATG TTACAGTAAT AATTTGCTTC TATTAACTAT AGATAATAGT
35401  TTTAGGTCAG GCACAGGAGT TCATGTCTGT AATTCCAGCC GTTTGGGAGG
35451  CTGAGGCAGA AGGATCACTA GAGCCCAGGA GTTCCTTATC AGCCTGGGCA
35501  ACATAGTGAG ACTTCGTCTC TATTTTTTAA AGAAAAAAAA AAAGATTAAA
35551  AAAATAGATA ATAGTTCCAA TCTTGTTGTA TCTTGTGCTG CTTTTGATTT
35601  GGCCAAATAA GGTTTGTCTT ATTTATATAG CCTTATAGAT TTAAATTGCT
35651  GATGGTAAAT ACCTCAAATT TTTTTTTTTC TAGGAAATTT TACCTGGATT
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FIGURE 3

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35701  GTTCTTAGGC CCATATTCAT CTGCTATGAA AAGCAAGGTA TGAACTTTGT
35751  TAGATTCATC AAGAGAGACT TTTATTAACC AACTTTTCTT GGGTAAGTTT
35801  TTTAGTAATA AAGAGTTTTA TTTTAGGGAG CATCCACAAA TACTGTCTGT
35851  TAACAGTAAT TGTCACTCTG GAGTACCTTC CTCTTTCCCT ATTTTACTAG
35901  ACCAGTAGTT CTCAAGTGTT TCACCACAAA TCAGAGTTTT TGTTTTTTCC
35951  TCATGAAATT TGTATGTTTG AAAGATTTAC CAAATAACTG ACCTTTAATA
36001  ACTTATTTAC TCTCTAAAAC ACTAGACATC TGTAATTGCT AATCATAGCT
36051  TCAGAACAAT ATGAGATGTA GTTAAAGCCC AAAATAAGGA ATTTCAATGT
36101  TTAGTTAAAC CTTCCTTATC AAGGGTAAGA CTGTGTGTGT TAATTGAAAG
36151  TCATTCACCT TAGTTCTGTT TTGCCAGCCA GACTTTAGAG AGCTAGTTGG
36201  TATCCCCGCT CTGAAATTTG AAACTTTTTG AGCACCAGTA TGTCACTCGA
36251  AGGAAATCCT CACTGGAGTA TTTCGGATTT CGGATTTTTG GATTAGGGAT
36301  GCTCAATTAT AAGTATAATG CAAATAGGCA AAACAAACAA ATCCAAACTC
36351  TGAAATATTT CTGGTCCCTG GCATTTTAAA TAAGGGATAT TCAATCCGTA
36401  TAGATATTCT ACATAGTCAA ACTTTAATGG ACTTACTCAG TTGCAGTTAA
36451  AATAGGTAGA TCTCATTTTA ATAAATATAG CAATGTTCTT GCCACTTCTA
36501  AAAGATTCAA TGCTACTAAT TCTCTTTGAG TTACAACGTG GAACATATCA
36551  CAGATGTCTT TCCCCAATAC TTTGCCTATT CAGAAGTCAG TATACTTAAA
36601  TTGTGTTTGA TATATCCATA ATTTAATTTG ATGTTCTTAG GAATTTAACC
36651  GGTTTTAAAA GGTCATTGAT TTTGAAACTG GAAGATTTTT TTGACAGTTG
36701  AGACATGGCT AAGAGTAAAC CTGGTCATCT TGATGATTTT TGCTTAGTTG
36751  GAAAGATAGG GAGTTAGTAA AAATAAGTAC TAGGGAAAGG ATAGGGCAGG
36801  TAACTATAGA CATAGCCGTA ATTTATTTTG TAAAAGACAG ATGTAAACAA
36851  GGTTATTGTC CATATAATTT GCTATTCACC AAGTACTAGT CTTCCAGATG
36901  GTTTTAGATA ATTTACATTT TTGAAATTCC CACTGTACTT TATAAATATA
36951  CATACAGTAT TTATCACATT AAATTAAAGT ATTTGTTTAA AGGTCTATCT
37001  CCTCAATGGG AGGCTGAGGC AGGCGGATTA CATGAGGCCA GGAGTTCGAG
37051  ACCAGCCTGG CCAACATGGC AAAACCCCGT CTCTACTAAA AATACAAAAA
37101  TTAGCTGGTT ATGGTGGTAC ACACCTGTAA TCCCAGCTAC TCACGAGGCT
37151  GAGGCGCGAG AATTGCTTGA ATCTGGGAGG TAGAAGTTGC AGTGAGCCAA
37201  CATGGCACCA CTGTACTCCA GCCTGGTTGA CAGAGTGAGA CTTTGTCTCA
37251  AAATGAAACA AAAACACGCA CAAAAAAAGG TCTAGTTCTT CAAAACTTCT
37301  TTTCTTGAAA TGTCACCATG GTCTTATTAG ACAGGAAAAG CCTCTGTGGC
37351  AGTTTATTTC CCACCCTAGG TAACCATAAT ATAGCCCATA TTTCTTTTCA
37401  TACCATTATC TAAAAACAAC AACAAAAAAT AATAATGGAG ATAAACCTAA
37451  ATGGATAAAC TCCTTTTTAA ACACTCATTT ACTGTTATTA TTTTGTGGGA
37501  GAGGAGTGGG GTCTTGCTCT GTTACCCAGG CTGGAGTACA GTGGCGCGCT
37551  CTCATAGCTC ACTGTAACCT CAAACTCCTG GGCTCAAGCT GTCTTCCCAC
37601  CTTAGTCTCC CAAGTAGCCA GGACTACGGG CACACACCAC CATGCCTGGC
37651  TTAATTCTCA AAGTTTTTGT AGAGATGGAG TCTGGCTATG CTGGCCACAT
37701  TTACTTAAGT ATATCTTTTT ATTAAATTCA AATACAGTTT AAATAAAAGG
37751  GACAAATTTA GGGCCTTTGT AATTAGTAAA CGGTTTGTTT TTGTAAAGTT
37801  TTTCTACTGT TTTTAAATGT GAGGTAAGGT CATAATTTGC TTCATATTAG
37851  GTTGGTGCAA AAGTAATTGC AGATCTGCCT CTGAAAAGTA CAAAATCTAT
37901  TCGCTGTTAC GTTAGGGCTC TATTTTGATA GTTTATTTTT ATTTAGTAGT
37951  AGTCTATTGG GCCTTCAAAA CTTGTTTAAG CATATTTATA CATAATTATG
38001  TGCATCGTCT TGTGCTTTCT CACATTCATA AAGTAGATAG GAAAACTCCA
38051  TAGGCATCAA GTGTAAACGA AGGACTTAAT GTTGAATTTG TTGTGGAAAT
38101  TGGCACAAAT CTCAATATAG AACATTGGTT AATTATTAAT CTTACCAAAT
38151  GCTTATCTCA CTTTCCCTAA CTCAAGTTAT ACTCAAGAAA TACAAAGATA
38201  ATTGAATTCT AATCTATGCT GACATAAAAC TTGCTGCAGA AATTAACACT
38251  TAAAACTTGC AAATTATATT GTCTTAGCCC AGGCTGCTCA AACAAAATAC
38301  CATAGACAGG GTGGCTTAAA CAACAGACGA TTATTTGAGT TCTGGAGGCT
38351  GGCAAGTCCA CAGTCATGGT CCGGCTCTGG TGAGGACCCT CTTGCTGGCT
38401  CGCAGATCCC TCCCTTCTTG CTGTATCCTC ACACGGCCAA GAGAACGAGT
38451  TCTTGCCTCT TCTTACAAGG GTACAATCCT GTCATGGAGG TTTCTACCCT
38501  CATGACCTCA ATCTAAAACT GATTATCTTC CAGAGACTCC ACCATCACAT
38551  CTTGGGGGTA AGGATTTCAA CATAAGAATT TGAGGTGATG CAAACATTTA
38601  GTTCATAACA CATATAAATT ATTTTTTTTT ACTTTGCTCA TGAATTATTA
38651  GTGCTACTGT TTTGTACTAT TTAAAATGCA GAAAATGGGA ATTAAATATA
38701  TAGGATTTAA AACAATGTGT CAAGAAATTC AAGGTTATCT GATTCTCATG
38751  CCATCGTGAC TTGTTAGTTC ATTTATTGAA CAGGTAATTA TTGAACAACT
38801  TAACTAGTTA TACATACTTG ATACTTAAGT GAATTGTATT ATACATTTTA
38851  CACATACTAT GTATCAGTGA ACAAATAAAA ATCTTTTCTG TCATGGAACT
38901  TAATGCTCTA GGTAATAAAA TAACATCTAT AAACTCACTT AAACTTATCA
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FIGURE 3

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38951  CTAGCAAATG AAAACTTATT ATCTGGTAAT TTCTAGAATT GTCATGTTAA
39001  ATTGCTTTAA GTATGGAGCC AAAAGCACTA CAGGTTGAGT ATCCCTAATC
39051  TGAAAAATCT GAAATGCTCC AAAGTGAAAC TTTTTGAGTG TCAGCATGAC
39101  AGCACAAGTG AATTCCACAC CTGACCCCAT GTAATGGGTC ACTGTCAAAA
39151  TTTTGTTTCA TGCACCAAAT GACTGTATGA AATTACGTTC AGAGTATATA
39201  TGGTGTGTGT GAAACATAAA TGAATTTTGT GTTTAAACTT GGATACCATC
39251  CCCAAGACAT CTGAGTATGT ATATGCAAAT ATTTCAAAAT CTGAAATCTG
39301  AAACACTTCT GGTCCTACCT TGGGACCAGC ATTTTAGATA AGGGATACTC
39351  AACCTGTATT GAATATAATA AGATGTCATT GAAGTTGCCA TTTTTAACTT
39401  CAGGAAAATT TTTAAATGGT AAAAGGTTAA TTAGATTCTG TGAAGTATGT
39451  AAATTAATTC TGACTCTTAA AGTATACTGG GAGAGGCAAG GAGTTGTCTA
39501  GAGATTTGGG TTCCAGTACT GCTGTTAACT AGGTCGGTGA TGTCCAAGTA
39551  TTTGGTAATG TAACTGTTTT ATGTCTTAGT GGTTCTCTCT AAACAATAAA
39601  GATTGCAGTC AATATATATT AACTACCATT TATTAAACAC TTGCTGTGTG
39651  TCCCAGGTGC TATGCCAAAC ATCTTACATA AAGGTTCCAT CAAGCTCTAA
39701  AATTGTAGGT ATGAAATATC CCTGTTAACC TTTTGAGGAC ATTAATGTAT
39751  TAATCTTGAA TCATTGAAAT ATCTTGCTGC CCACTTCAGG TATATTATAA
39801  AATTAGCTTT AATTCCCTGG ACTTAAGCAG AGATGTGGGT TCTGTGTATT
39851  TTCAAACATC TGTGTTATAT AGTAAGATGA TGTTTGATAT TTTAAAATAT
39901  TTATCTTCCC TGTCCTCCCC CTGCTTTTTT TTTTATACAG CTACCTGTAC
39951  TACAGAAACA TGGAATAACC CATATAATAT GCATACGACA AAATATTGAA
40001  GCAAACTTTA TTAAACCAAA CTTTCAGCAG TTATTTAGGT AAGAATTATT
40051  GCTATGATTT GTAAAACACT TAATGAAGTT TCATTTCAGG TTTTGTACCA
40101  TCAGTTGTTT CTGTACATAT CTAGTTTGTA AAAATGGGTC ATATAGTACA
40151  TAGTTTTTTA AAATAAATTT TACTTAAAAT ACTTAAATAA ATTATGCCCA
40201  TAATGCAGAA TTCTAAAGGT TCAAAAGAGT GTATATTGTC AAGAAGTTTC
40251  TGGGAAAGTA AAAATAAAAA AGAATTTAAA AATAATGTAT ACTGAAAAAT
40301  AGGTTTTAGT GTACATTATT TTATCTCTTG AGGGATAAAG GAATTGAGTA
40351  TCTAGGGGAT AGGTTTAGGG AAACAGCATC TACTGTTACC TCTTTATTGG
40401  GTAGTTTTTG AGTGTTAGGT TAAATTTATG AGCATAGTCT TATAGATAAA
40451  TTTTTTTTTA CATTGGCTTT CTTTTTTACT TTATATTTTT TGGAGATTGG
40501  TTTATATCGG TATGTATATC AAACTGCTTA TTCTTTTTAA GTTGCATTGT
40551  AATCCATTGT ATGGCTATAC TAAAATTTAT TCAATTAGTC TGTTAGATAT
40601  TTAGATTGTT TCTGGCCTTG TACTAATATG TATAGCATAT AGTGACTATC
40651  ATTGTACATA TTACTCAATT TATATGTGAG CATATTGATA GGGCTTATTT
40701  GCAGAATTGC TGGATATAAG AGTATGAACA TTTTAAATTT TGATAGATGT
40751  TGCAGATTGT TTTCCAGTGC GTTGTATCAG TGTACATTCC CATTATCAAG
40801  TATGTGAGAG TGACTCTTCC CTTAGTATCT CTCCAAGACG GAATTGTGAA
40851  ACATTTTTAA TTTCTCAAAG TCTAATGGAG TAAAAATGGT ATCTCATTTG
40901  ATGTTCTTAT TTATCTTGTA AGTTCAGTTG AGCATGTAAT GGTTTTTAAT
40951  GTTCTTTATT TTAACTTCAT TTTTAAAATA GAGTATATTA CGCATGGTAC
41001  AAAAGTGAAA GGATATGTAA ACATATATAA TGAAAGTAAC TCTACTTTTT
41051  CTCTTAACCC AAGCCACCTT GCTCCTATCC TGGGAGGCAG CTTCTTCCTT
41101  CAATATCTAT GTAAAAGTAT ATATGTTAAA AATATTTTAG GCCAGCACGG
41151  TGGCTCACGC CTGTAATCCC AGCATTTTGG GAGGCCGAGG TGGGCAGATC
41201  ACCTGAGGTC AGGAGTTCGA GACCAGCCTG GCCAACATGG CAAAACCCCA
41251  TCTCTACTAA AACAAAAATT ACCTGAGCGT GGTGGCACAT GCCTGTAATC
41301  CCAGCAGCTC AGGAGACTGA GGCAGGAGAA TTGCTTGAAC CCAGAAGGCA
41351  GAGGTTACAG TGAGCCGAGA TCACACCACT GCACTCCAGC CTGGGCAACA
41401  GAGCAAGACA CCGTCTCAAA AACAAAACAA AACAAAACAA AAAAAAAACA
41451  GTGCTGTGGC TTACACCTAT AATCCCAGTA CTTTGGGAGG CTGAGGAGGG
41501  TGGATCACGA GGTCGAGATT GAGACTGTCC TGGCCAACAC AGTGAGACCC
41551  CGTCTCTACT AAAAATACAA AAATTATCTG GGCGTGGTGG CACATGCCTG
41601  TAGTCCCAGC TACTCAGGAG GCTGAGGCAG GAGAATCACT TGAACCTGGG
41651  AGGCAGAGGT TTCAGTGAGC CAAGATTGCC CCACTGCACT CCAGCCTGGC
41701  GACAGAGCAA GACTCTGTCT CAAAAATAAA AAAAAAAATT TAATGCTCTG
41751  CTTTATTTTT ACAATGAAAC CAATCTATAA ATATCTGTAA ATACAAGATA
41801  CATACTCTAA AATACATTGT GTGAACATAT AATAGAATAC TATGTAACCA
41851  TGAAAAAGAA TGAAATATAT GTATGTGTTT GGATTTGGGA TGATCTCCAA
41901  GATAATGCAT TACATGAATA AAGCAGGGTG TGGAACAATG TATATATTTG
41951  CAATGTGTTG AGTAAATATA TATATACTAC ATTCCATATA TTTATTCTTA
42001  ATATATGCAT AGAAAATTTC TGGACCAAGA GGCTAGAAAC TTCATAGTGA
42051  TTGCTTCTAA GAAGGAAAAT TCAGGGCCTG TGATGGTAGA GGGACGTATT
42101  TTTCTTTCGT TTTTAATTTT GTTTTTTTTT GTTGTTGTTG TTTTTTTTTT
42151  TTTTTTGAGA TGGAGTCTCA CTCTGTCACC CAGGCTGGAG TGCAGTGGTG
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FIGURE 3

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42201  TGATCTTGGC TCACTGCAAC CTCTGCCTCC TGGGTTCAAG CGATTCTCCT
42251  GCCTCAGCCT CCTGAGTAGC TGGGATTACA GGCATGTGCC ACCACACCCA
42301  GCTAATTTTT TTTTTTTTTT TTTTTTTGGA CAGAGTTTCG CTCTGTTGCC
42351  CAGGCTGGAG TGCAGTGGCA TGATCTCGGC TCACTGCATC CTCCGCCTCC
42401  CAGGTTTAAG CAATTCTCTG CGTCAGCCTT CTAAGTAGCT GAGATTACAG
42451  GTGCCCACCA CCACTCCCAG ATAATTTTTT TTGTATTTTT AGTAGAGACG
42501  GGGTTTCAGC ATCTTGGCCA GGCTGATCTT GAACTCCTGA CCTCTTGATC
42551  CACCTGCCTC AGCCTCCCAA AGCACTGGGA TTACAGGTGT GAGCCACCGC
42601  ACCTGGCCTA ATTTTTGTAT TTTTAGTACA GACGGGGTTT CACCATGTTG
42651  GCCAGGCTGG TCTCGAACTC CTGACCTCGT GATCTGCCCA CCTCGGCCTC
42701  CCAAAGCACT GGGATTTACA GGCGTAAGCC ACTACGCTCA GCCGAGGGAC
42751  ATATTTTTCA TGGTACCCTT GATATCCATG GGGGATTGCC TCCAGGAACC
42801  CCCATGAATA ACAAAATCCT CAGATGCTCA AGTCCCTTAT ATAAACTGGT
42851  GTAATATTTG CATATAACCT GTGCACATTC TCTCATATAC ATTAAATCAT
42901  CTCTAGATTA CTTCTAATAC TTAGTACAGT GTAAGTGCTG TGTGAATAGT
42951  ATTGGATTTT ATTTTTATTA TTTTTAGTGT TGTATTTTAC CTTATTTTTT
43001  GTTAATGTTT TTTATTGTTG TCGGTTGAAT CCACAGGTAT GAAATTCTTG
43051  GATATGGAGG GCTGACTCTT TACTTTTGTA GTGTTTTTTT TTTACACCAT
43101  ATTTAGTTTA TTAAAACTAG TTATTAAAAA GGAATATCCC AAAACACTGA
43151  TTTTTTTTTT TTTTTTTTTT TTTTTTTGAG ACAGAGTCTC GCTCTGTCAT
43201  CCAGGCTAGA ATGCAGGGCT CACTGCAACC TCTGCCTCCC AAGTTCAGGC
43251  AATTCTTCTG CCTCAGCCTC CTGAGTAGCA GAGATTACAG GCATGTGCCA
43301  CCACGCCTGG CTAATTTTTG TATTTTTAGT AGAGACGGGG TTTCACCATG
43351  TTGGTCAGGC TGGTCTCAAA CTCCTGACCT CGTGATCCGC CTGCCTTGGC
43401  CTCCCACAGT GCTGGGATTA CAGGCGTGAG CCACTGCGCC CGGCCTGAAT
43451  TTTTTATAAT TATGAAAGAA ATACTTTTTT TTTTTTCAAA GATAGGATCT
43501  TTCTCTGCTG CCCAGCCTGG ATTGCATTGG CATGATTTCT GTTCATTGTA
43551  GCCTTGACCT CCCAGGCTCA AGCAATCTTC CTGCCTCAGC CTTCCAAGTA
43601  GCTGGGACTA CAGGTGCACC ACCGGATCGG GCTAATTTTT TTTTTTTTTT
43651  TCTAGAGATG GGGTTTTGCT GTGTTGCCCA GGCTGTTCTT GAACTCCTGA
43701  GCTTAAGCGA TCTACCCACC TCAGCCTCCC AAAGTGCTGG GGTTACAGGC
43751  ATGAGCCACC ACACCTGGCC ATGAAACACT TATTCTTTAT AAGTACTTCG
43801  GAAGGTATAG AATGACACCA AGAAAAATAT TTAAATCATC TACAGTTCCA
43851  CAATTCAGAG AAAACACTTT TGTTAACATT TGGAATATTT CCTTTTAAAT
43901  CGTTCTCTGT TGTGTATGTG TATTTACGTA TATATGCATA GAATTATTAA
43951  AGAAAATGAG AATGTTGTAT TTTAAAATAT CAAACTATAT AAGGTGAAAC
44001  TAATCTTAAG AAAAAACAAA AAAGCCAAAA AATCATACTA TTCATTTCTA
44051  ATGTGTACAG ACTTTTTGTT TTAAATTATA ATGTTGTTTG TGCAGGTTCT
44101  TTATCCTAAT GGAAGAACCA TTTCTCCTTA AACTTTTACA ATACTAGCTT
44151  CTTAGAGATT GATAGTTCTA CTAGCAGTGC TTGACACTGA AAATGTTATG
44201  CGTTAAAATA TTTAATTTCA TTCTGAGTTA ACATTTTTCC CCTGAAGCAT
44251  TATTTTATGT AACTGGAATA CCCAGTCACT TCAGGATACA GTCATTGTCG
44301  AAATCCTTGT AGGTTAAATA TTGGATTTTC CTCAGATCCT GAGGTTCAGC
44351  TTCTGTGTTT TTTTTTGTTT GTTTTTTTGT TTTTTTTTTT TTGTTTTTGA
44401  AACAGAGTCT TGCTGTTTCA CCCAGGCTGG AGTGCAGTGG CACAATTTTG
44451  GCCCACTGCA ACCTCTGCCT CCCGGGTTTA AGTGATTCTC CTGCCTCAGC
44501  CTCCTGAGTA GCTGGGATTA CAGGTGTGCA CCACCATGCC TGGCTAATTT
44551  TTATATTTTT AGTAGAGATG GGGTTTCACC ATGTTGGCCA GGATGGTCTT
44601  GAACTCCTGA CCTCAGGCAA TCCACCTGCC TCGGCTTCCC CAAGTGCTGG
44651  GATTACAAGC ATGAGCCACC ATGCTCAGCC TCAGCTTCTC TGTATTAAAG
44701  TCCTGAATTC TTTGAAGTTG TTACCACCTA AATGATCATT GAAAAACTGT
44751  ATTTTTTAGT GCAAAATTGT TCTTAAAACT AATTTAATAA CTTAGCTAAT
44801  TGCCTATAGT TGTGTTAATA AACAGTGGTC TTAGAAACGC TTAGAAATGG
44851  AAGTTTTTTA CAAAAATAAG CTAACATATT TAAAATGCCT TTTAAGTATT
44901  TTGTAAAGTG TAAAATTCAG TACAGGTGCT CTCTCAGCTA GTTTTTTTTT
44951  TTTTTTTTTT TTCCCCTTTA CTAAAGATGA GTTCAAACAG TGAATGTTTG
45001  ACTCCTGGTT CCATAGACCA TACCTTCCGT TTTTATTTGT TCGTTCTCTT
45051  AGACTTTGGA CTTCCTCTGA AATGTCCTCT GTAGGTTCAT GAGCAGGAGT
45101  CACAGGACCA CTTAGAGAAC AATCTTCTGG TCTTAGAGAA ATTGGTAGAA
45151  ATAAAAGAAT AACATAACGA TTACAGGTAC TTTTGTCTTT ATTTCTAGGT
45201  CCACTCTAAT CTAGAGGAAT GTATCTTCCT GCTTGTGATT TTTCTATTTT
45251  AACCAGATGG TTCATTATAT GCAAATAAAA TATGTATTTA TTTTTGAGAT
45301  AAGAATCTTG CTCTGTTACC CAGGCTGGAG TGCAGTGGCC CAATCACAGC
45351  TTACTATATC CTTGACTTCC AGGCTCACAC AGTTCTACCT CAGCCCCCTT
45401  AGTAGCTGGG ACTATAAGTG CACACCACGA CACCCAGCTA ATTTTTTAAT
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FIGURE 3

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45451  ATTCTGTAGA GATGGAGTCT CCCTCTGTTG CTCAGGCTGG TCTCGAATCC
45501  CTGGGCTCAA GTGATCCTCC CACCTTGGCC TCCCAAAAGA GTTTCTTTTT
45551  GCTGGGATTA TAGGCATGAG CCCATTGTGC CCAGCCTGAT GGATTTTTTA
45601  AATACTTAAA TATCAGAGAT GTTAACATGG TGTTTCAGGT TTTAATGCCT
45651  TCAAGCAATG TAAAATCTAC CACACAGTTC TTGGGAATAT GATACTTTGA
45701  AAGTTGTTTT GCATTCTTGC CATGGTTAAC AAGAAATAAT GAGTTATTTT
45751  TTTAAAGTAC CTTAAGTGTT TTACTTAAAG TGTGCTTATC ACAAAATACT
45801  CTATTTTCAG ATATTTAGTC CTGGATATTG CAGATAATCC AGTTGAAAAT
45851  ATAATACGTT TTTTCCCTAT GGTAGGTACC AGTATTTTTT AAATATCATT
45901  TAAAATTTAT TTATGATTTG ACTTCTTAGT TGTGCTTTTT TTTTTTTTTT
45951  TTTTTTTTTT TTTGAGACAA GAGTTTTACT CTTGTTGCCC AGGCTGGAGT
46001  GCAATGGCGC AATCTTGGCT CACCACAACC TCTGCTTCCC GGGTTCAAGT
46051  GATTTTTCTG CCTCAGCCTC CCAAGTGGCT GGGATTACAG GCATGAGCCG
46101  CCATGCCCAG CTAATTTTGT ATTTTTAGTA GAGACGGGGT TTCTCCATGT
46151  TGATCAGGCT GGTCTCAAAT TCTCGACCTC AGGTGATCTG CCTGCCTCAG
46201  CCTCCCAAAG TGCTGGCATT ACAGGCGTGA GCCACCGTGC CCAGCCCCTT
46251  TAATTGTGCT TGTAAAGCTT GCTACTTTTA CTTTGCTATG ACTGAAAATT
46301  ATGTGATTGT GTTTTTAAAA GAATTATTTG TAGAAAATTT TTTATGATCT
46351  CCAGAAATTT GAGGAATCAT ATTGTGAATG TATTGGACTT AAATTAAATT
46401  TTGGCTTCTT TAATTTTTTT GGACTTGTAA TAGTTCTATT TATAGCATTT
46451  TGGAAATTGG TGAATCAAAA TAATTTTTAT ACATATAAAT TAGGAAATTG
46501  TTTTCAATAG GTTTCATTTT GTTTCATTAT ATGCATTTAT TTTATGCTTA
46551  CATTAATCCA CATGTCTTTT GCCTCCAGAC TAAGGAATTT ATTGATGGGA
46601  GCTTACAAAT GGGAGGTAAA TAACATTTCC TTTCCTTAAC TAATGTTTAT
46651  ATTTTGATTA TTTGTTAATT TTTTAGTTGG TATTTGTCTT AAATGCAGGA
46701  TATGGAAGTT ACAATTATAT GTAGTAGCTT ACTCCCAAAT TTGTATTTTC
46751  CCAATTACTT GTTTCATTTG GATAGGCTTT CTGGAGTATC CCTGTAGACT
46801  GTTTTCAAAT TCTCTGTGAG CTTTCAGTTT CTTTAATAAG AGTCTGCTAT
46851  ATTCTCTACA CAGTTGATAA TAACAAATTG TAAAGATTTG AAGATATCCA
46901  AGTGATTATA GTATATAAGG AGTTACTTTA CTGTGGTTTC AATGTAGTTC
46951  AGCTACTGAC TCAGGTGTTT TTCTATTAGA ATAATGAATT CATGTTTTTC
47001  AGGAAAAGTT CTTGTGCATG GAAATGCAGG GATCTCCAGA AGGTATGAAG
47051  TTAGAAATAA TCTTTCTTTC TATAACATTT AATTAATGGG CTGTATTTTC
47101  TGGTTGTTTT TAAAATTATT TTCCCCTCTT CAGTGCAGCC TTTGTTATTG
47151  CATACATTAT GGAAACATTT GGAATGAAGT ACAGGTAAGA AAATACCCTA
47201  AAACCTAGCC ACAGTTTAAA TTCTCATTAA AATGAAACTT AATGGGAATA
47251  GTTTGGAAGT TTGAAGTTCT TATTCCCCTG ATTATTTTTC ATGTAGTCAT
47301  GTTTGATTAG GCAGGCCCTT ATTCCATGAT TAGTCTTAAC CTAATTTATC
47351  TACTTGTATA GATATGCATA GGCTAATATG GAAATCCTAT GGAAAACTAC
47401  TTACCTACCA CAAGGGAATT GGTTGGTATG AGTATAAAAA CTCGTGACCA
47451  CAAATGTTAG TGCTTGCCTT ATTTAAAGGG CTAATTTATC ATGTTCTCCT
47501  TTAACAATAG TTGGATGAAA AATTACCTAG GAATTGTTTG CAGCATCTAT
47551  TTACAATTCA GAGTAGTCTT TCTTATCAAA AATCATCTTT TCCAAGCATT
47601  CTGTATAGAT TTTTTAAAAG ATAGGGGGTG GTAATGAGCT TCTTGCCCCC
47651  AAGACAAAGC AAAAGCCTGG GCCAGTGTAC AGTATTTCCT TTCTCAGCTT
47701  TTCTTGTTCT ACAAATTAGA AATCTTATAG TAATCATTGA CACATCTTTC
47751  TATTTCAGTC CCCTTTTATA TCTAAATTAG AATGGATAAC TTTGCTTAAA
47801  AATATCTATT CTTAAAGGAA TATTATTTGA ATACAAATAT TTATTTATTT
47851  ATTTTTGAGA CGGCGTCTTG CTCTATTGGC AGGCTGGAGT GCAGTGGTGC
47901  GATCTCAGCT CACTGCAACC CCCGCCTCCC AGATTCAAGC AATTCTCCTG
47951  CCTCAGCCTC CCTAGTAGCT GAGACTACAG GTGCACACCA CCACGCCTGG
48001  CTAATTTTTG TATTTTTATT AGAGATGGGG TTTCACCATG TTGGCCAGGA
48051  TGGTCTCGAT TTCTTGACCT TGTGATCCAC CTGCCTCGGC CTCCCAAGGT
48101  GCTGGTATTA CAGGGGTGAG CCACTGCACC CAGCCAGAAT ACAAATATTT
48151  AATTGAAAAA AGATTAAACA TGTATTGATG GACTTTATGT TTTATATATT
48201  GTTTTTATTA TTTCGAATTT TGTCAGACCA TTAATGTTGG AAATAACTTG
48251  TATTTATTGG GTCTCTGCTA TGAGCTCAGT ACTATTATAG GCACTTTAAG
48301  CCTCATAACA AAAGTAAATA AACCTCTTTA ACCAGTGATA GTATTTTGAG
48351  CTTGAACTTG TACTATATGC ACAAAATGCT TACATTTTAT ATATTTATTT
48401  TAGAGACAGG GTCTTCCTTT GTTTCTCAGG CTGGAGTGTA GTGGCACAAT
48451  CATAGCTCAC TGTAGTCTCA GACTTGAGGA CTCAAGTAAT CCTCCCACCT
48501  CAGCCTCTCA AGAAGCTGGG ACTATACCAC ATCACTGTGC CTGGCTAATT
48551  TTTAAGTTTT TTGTAGAGAT GGGGTCTTAC TACATTGCCC AGGCTGGTCT
48601  CAAAGTCCTG GCTTCAAGCA GTCCTCCTGT GTTGGCCTCT CAAAGGATTG
48651  GGGTTACAGG CAAGAGCCAC TGCACCTGGC CACTTTACAC TTACCTCCTA
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FIGURE 3

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48701  TTCATAGTAG TTCCCCAAGG TAGGTGTTAT TAGACTCTTC ATTTTACCAA
48751  TGGACAAAAT AGAGCTTAGA GAAGTTGAGC AAGCTGCCGT AAGCATATAG
48801  CTGGTGAGAA AAGGAATTGT GATATTTAAT CTCATCATGC TTTTTCCATT
48851  ACAACTCATT ACCCCTCTCT ATTGCTAAGT TGTATGATTA TGATTAATTC
48901  ATTAAATAAT GCTATCACAT TAACACTCTT TTTCTGTTTT CAGAGATGCT
48951  TTTGCTTATG TTCAAGAAAG AAGATTTTGT ATTAATCCTA ATGCTGGATT
49001  TGTCCATCAA CTTCAGGTAA CTTTTCTTCC TCTTTAAGGC AATCAGAAGT
49051  AAGATATAAA ATCTTTTATA CATGTAATTT AGGTGTACAA TTTACTTTGT
49101  GAATACTTAA AATTGCCATA ATCTGACTAC TTTGATGCTT TATTCAAGTT
49151  TATATCTCTA TTTAGAAGTA TTTTCTTGGC TGGGTGTGGT GGCTTATACC
49201  TATAATCACA GCACTTTGGG AGAACAAGGC ATTTGGATTG CTTGAGGCCA
49251  GAAGTATGAG ATCAGCCTGA GCAACAAAGT GAGACCCAAT CTCTAAAAAA
49301  TAAAAAATTA AAAAAAAATT AGCCAGTCAT GGTGGTGCAT GGCTGTGGTC
49351  CCAGCTACTC AGGAGGCTGA GATGGGAGGA TTGCTTGAGC CCAGGAGTTT
49401  GAGGCTACAG TGAACAGTGT GTCTTTGCAC TCCAGCCTGG CCCACAGAGT
49451  GAGACCCCAT CCCTAAAAAA TTAAAAAAAC TTTTTTTTCT TAAAGGCTGG
49501  CATTACCAAG AAAAAAGGGT TAAAGACACA TTATCAAATC TAAAGTAAAA
49551  TAATTGCTGT TAGAAATGTC TGATTTTTTT TTGTTGTTCA TTTTGATCAC
49601  ACAGAGCATA AGACAGTTTT GATTCTAAGT ATACTAACTA TAACAGCTTT
49651  TTCTATTCTA TGTTTATCTT TTCCATGTTG TTTCATATTT TGTTGATGCC
49701  TGGCAGATGC ACTGACAAAG ATGATAAGTC TATGAATTAA CCTAATTAGA
49751  CCACGTTGCT CAGTTTATTC CAAGAGGCAA AATCATAGGC TGCAGAATGT
49801  GCTCTGGCTA ATTACATCCA ATTATGTAGG AATAAAGCTC ATGTTTCAAC
49851  ATCAAGAATA TTTATTACAA AATATATTGT TATAGTTACC AAGGTTTAAA
49901  TTTTATTTTA ATATTTAATT TACTTTTAAT TTTTACTACA TTCAAAAGAG
49951  AAACAGTGTC ATCTGTGTTC AGCCTGTTCA TGTAAAATGT TTGTCTTCTA
50001  ACTTTGTAAG TTTCTTTGCC TTTTACCATG TTGTAGAAAA CATTGTTTTT
50051  TTTCATTTTT TTTAAACTAT TTTTTAAGCT TTTCTTTTTT TTGTGGATAC
50101  ATAGTAGGTT AGGTATTTTG ATACAGGCAT GCAATGTGTA ATAATCACAT
50151  CATGAAAAAA TAGAGTATCC ATCCCATCAA TCATTTATCC TTTGTGXXXX
50201  XXXXXXXXXX XXXXXXXXXX XXXXXXXXXX XXXCCTCCCA AGTAGCTGGG
50251  ATTACAGGCA CGTGCCACCA CGCCCAGGTA ATTTTTGTAT TTTTAATAGA
50301  GATGGGATGG CCGGGTGTGG TGGCTCACGC CTGTAATCCC AACACTTTGG
50351  GAGGCTGAGG TGGGTGGATC ACCTGAGATC AGGAGTTTGA GACCAGCCTG
50401  GCCAACATCG TGAAACCCTG TCTCTACTAA AATTACAAAA ATTAGCCAGG
50451  CGTGGTGGCA GGTGCCTGTA ATCCCAGCTA ACNNNNNNNN NNNNNNNNNN
50501  NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNTGCTGGAA AGGGATCACC
50551  TGAGTATCAG GAGTTTGAGA CCAGCCTGGC CAACATCGTG AAACCCTGTC
50601  TCTACTAAAA TTACAAAAAT TAGCCAGGCG TGGTGGCAGG TGCCTGTAAT
50651  CCCAGCTACT TGGGAGGCTG AGGCAGGAGA ATTGCTTGAA CTCGGGAGGC
50701  GGAGGTTGCA GTGAGCCGAG ATGGCATCAT TGCACTCCAG CCTGCGGAAC
50751  AAGAGCAAGA CTTCGTCACA AAAGAAAAAA AAAAATAGAG ATAGGGTTTT
50801  GCCATGTTGC CCAGGATGGT CTTGAACTCC TGACCTCAGG TGATCCACCC
50851  ACCTTGGCCT CTCAAAGTGC TGGAATTACA GGCGTGAGCC ACCACTCCTG
50901  GCCCAAAAAT GTTTTATCAG ATTTTTGTGA TCATTTGTTG GTGTTCCTCT
50951  CACCGGTTTG TAAGAGCTCT TTTTATATTA TGGAAATCTA TTTATAGCCT
51001  ACCGATTTGA AATATCATTT TTATTTTATA CCAAATTCTG ATATGTCCTT
51051  TAGAAGTTTG AAGTTTTCTT TTTTAAGGTG CTTATGGAAT GGCTAGTTCT
51101  AGTTTTTGAA CCGTTAATAT GGTGACTTGA GTTACTGGAT CACATTAGAT
51151  TGGATTTCCT AATATTGAAT CATCCTTTTG GTCCAGCAAT GGATCCCACT
51201  TGGTTATGAT AGACTGTTCT GTTAATGTAT TGCTGGATTG TATTTGCTAA
51251  TCTTTTTGTT CAGGATTTTG GAATCAGTTA AATAGTAAAT TGGTTTGTCT
51301  TTCTTTTTTT TTTCTGTACT ATCCTTTTCT GGTTTTACTA TCTCTGTCAC
51351  AGTGTTCTCA TTTTTTAGTG GAAGCTTTCC ATTTCTCTTT GTGCCATGGA
51401  TCAATTTAAA TTAGATTGGA GTTACTTGTC TCTTAATGCA TTAGTATATG
51451  GCACCTGTGA AATATCTGAC CATAATGTTT TATCTAATTC AGTTATTCAT
51501  TATTTCATTC ATTCATATAT TTTGACAATA GACCAGTTCT CAGACAACAT
51551  TCTTCATTTG GTGTATCGGT TTGATTTTTT CTTTTCTTTC TTTCTTTCTT
51601  TCTTTTTTTT TTTTTTTTTT TTTTTTTTGA GGCAGAGTCT TCTGCTCTGT
51651  TGCCCAGGCT GGACTGCAGT GGTGCAATCT CAACTCACTG CAACCTCTGC
51701  CACCTGGGTT CAAGTGATTC TGCTGCCTCA GCCTCCAAAA TAGCTGGGAT
51751  TTACAGGTGC CTGCCACCAC AACTGGCTAA TTTTGTATTT TCAGTAGAGA
51801  CGAGGTTTCA CCACATTGGC CAGGCTGGTC TCAAACTCCT AACCTCTGGT
51851  GATCCGCCCG CCTCGGCCCC CAGAGTGCTG GGGTTACAGA TGTGAGCCAC
51901  TGCTCCTGGC CTGGTTTGAT TTTCTGATAC CCCTCAGGTC ACTTTGGATG
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FIGURE 3

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51951  TATTTATGAT CTTCTGTGTA ATCATTGATT TCATAAGAGT TCTACATAGA
52001  ATTAAGGAAA ATAATATCTT GTACTTTAAT ATCTTTTGGT TCTATTATTT
52051  TTTTTCTTCA TCTGGTTAGT CCATGTTGTT TTTCTGTATT CTAATTTCTG
52101  CTTCCTTGGT ACTTTGCTTT AGTGTTGTTT GCTGCTGCTG TTGTGAATTT
52151  CCTGAGTTGA AAACTTGGTT TCTTTTTATT CTTTCAAAAA TTCAAGGCTA
52201  TTAATTATCC TCTTTGCATT GTGTTAGTCG CATGCTGCAG ATTCTCATCT
52251  GCATTATTTT TATGTTATAG CTTGATATTC TGTGATTTCA GTTTTGGTTT
52301  CATTTTTTAT CTAATATGTG TTGAGATTTT TTTTATTGTA TAGGTGACTG
52351  GGTTTTAAAT TTTTTATTTT TGTTCATATT TAGTTTTATT ACATTGTAAT
52401  CACAGAATGT TTTGTAGTAC TTGTATTTTT TGATGTTTTC TTTGTGGTTT
52451  AATATGTAGT TGTTTTCATG AATTTTATGG GCATTTGAAA AGAAGATGCA
52501  TTCTGTTTTC AGGGGATAAA GTTAAATGTA TTTGTCCACT TGATCTGTCT
52551  TGGGCTGAAA TCAGTGAATT GAAATCTTTT ACTATATTGT GTTTATTTTT
52601  TCTTTATTTC CCCTTTTTTG GTTCTGCAAG TTTTTTTCTG TACTTAACTA
52651  TTTGGTACAT AAAAATTCAA GTTAGGTTTT TATTTTAGTT GTACCCTGTT
52701  TAAATTTCAG GGTTTTTTGT TGTTGTTGTT GAGACAGAGT CTTGCTCTGT
52751  GGCCCAGGCT GGAGTGCAGT GGTGCGATCT CGGCTCACTG CAACCTCTGC
52801  CTCCTGGGTT CAAGTGATTC TCCTGCCTCA GCCTCCCAAG TAGCTGGGAT
52851  TACAGGCATG CATCACCACG CCCGGCTAAT TTTTGTATTT TTAGTAGAGA
52901  CGGGGTTTCA CCATGTTGGC CAGGCTGGTC TCGAACTCCT GACCTCATGA
52951  TCCTCCCACC TCGGCCTCCC AAAGTGCTGG GATTACAGGT GTGAGCCACT
53001  GTGCCTGGAC AAATTTCGGT TATTTTACCT TGCAGTTAAC CTCGTTTAAT
53051  ATTGTGAATC CTACTCTTTC TGTTCGCTTG CTACCTTTTG AGTTTTCCCA
53101  TTCCTTTTCC TTCAAGCTTT CTAAATCACT TGATTTTAGA TGCTTTTCCT
53151  CAGTGTAGTC TAGGATTGAG TTTTGCTATT AGATTTGGTA TCATTGTTTC
53201  CTAATAGGTG AATTTAACCC ACTTTCATTT ACTGAAAATG ACAGATACAA
53251  TCTTATCTAT TATTATTTCA TATTATGCTT TCTGTTTTAA ATGAATCCTT
53301  TTTTTAACCT TCTGCTATAG TTTAAAATTT TTTGGTGTGT TTATGTTTGT
53351  TACATAATTT TTAAGGTTTT ATTTATTTAC TTTTCCTTTT TTTTTTTTT
53401  TTTTTTGAGT TAGAGTCTCA CACTCTTGCC CAGGCTGGAG TACAGTGGTG
53451  TGATCTCGGC TCACTGCAAC CTTTGCCTCC TGGGTTCAAG CGATTCACAC
53501  ACCTCAGCCT CCCGAGTAGC TGGGATTACA GACATATGTC ACCACATCCA
53551  GCTAATTTTT GTATTTTTGG TAGAGACGGG GTTTTGCCAT GTTGGCCAGG
53601  ATGGTCTCGA ATTCCTGAGA TCATGTGATC CACCCGCCTC AGCATCCCGA
53651  AGTGCTGGGA TTACGGGCGT GAGCCACGGC GCCCAGCCCC TTAATCCTAC
53701  ATTTAAATAG GGATTCAGCC CAATCCTATT ACCTGTTTCC AGGGGTCTTT
53751  ATTAAACTCT TGGACTTTAT TAAGAATAGT TTCATGGAAA CTATATTCCC
53801  AGGGAAAACT ATCCCTTTGC ATATTGGAAA AATATTTTTC TTTTTGCCCT
53851  TATATTTGAA TGACAGTGGC TAGATATAAA ATAGGTATTT AATACTTTTT
53901  CCCTAGTGAT TTTGTACACA GACCTGATAT TAAATATTTT TTGTTTGTTT
53951  TTTATTTTTT GGAGATGGAG TCTCACTCTG TCGCCCAGGC TGGAATGAGT
54001  GCAGTGGTAC AATCTAGGCT CACTGCAATC TCCACCTCCC GAGTTCAAGT
54051  GATTCTCCGC TTCAGCCTCC TGATTAGCTG GGATTACAGG CACATGCCAC
54101  CACACCCAGC TAATTTTATA TTTTTAGAAG AGATGGAATT TCACCATGTT
54151  AGCTAGGCTG GTCTCAAACT TCCGACCTCA GGTGATCTGC CCTCCTCGGC
54201  CTCCCAAAGT GTTGGGATTA CAGGTGTGAG CCACCGTGCC TGGCCTAAAT
54251  ATTGTTTTAG AGAAGTTTGA AGGCAGACCA ATTTTAAGAT TCCCCCCTTA
54301  GGTGAATTGA TTTGTATCAG GAGAAGGTTG TCTAGATCAG CAGTCTCCAA
54351  CCTTTTTCAC ACCAAGGACC AGTTTCATGA AAGACAATTT TTCCACGGAT
54401  GGGGTGGCGG GGGAGATGGT TTCAGGACAA AACTGTTCTA TATCAGATCA
54451  TCAGGCATTA GTTAAGGAGT GTGCAACCTA GATCCCTCGC ATACCATAGG
54501  GAGGGATAGG TTTACCATAG GGTTTGCGCT CCTGTGAGAC TCTAATGCTG
54551  CTGTTGATCT GAGAGGAGGT GGTGCTCAGA TGGTAATGCT CCCTGGAGTG
54601  CCACTCACCT CCTGCTGTGT GGCCTGGTTC CTGACAGGCG ATGGACCGAT
54651  TCTGGGGTCT GCAGTCCAGG GGTGGGGACC CTCATCTAGA TGACCATAAG
54701  ATGCTTTATC AAGGTGTATC CTGGTTTTTT ATGTTTTTGT TTTTTGAGGG
54751  GGTCTCGCAC TGTCACCCAG GCTACAGTGC AGTGGCGCGA TCATGGTTCA
54801  CTGTAGCCTT GACCTCCTGG GCTCAAGTGA TCTTCCCACC CTAGCTTCCT
54851  AAGTAGCTGG GACCATGGGT GCACACTATC ACACCTGGCT AAGTTTTTTG
54901  TTTGTTGTTG TTTGAGACAA AGTCTCACTC TGTTGCCCAA GTTAGAGTGC
54951  AATGGGGCAA TCTTGGCTCA CTGCAACCTC TGCCTCCTGG GTTAAAGCGA
55001  TTCTTCTGCC TCAGTCTCCC AAGTTGCCAG GATTACAGGC ATGTGCCACC
55051  AAACTCAGCT AATTTTTGTA TTTTTTGTAG AGAGACAGGG TTTCACCATG
55101  TAAGCCAGGC TGGTCTGGAA CTGCTGACCT CAGGTGATCT GCCTGCCTCG
55151  GCCTCCCAAA GTGCTGGGAT TACGACGTGA GACCACACAC CTGGCTTAGT
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FIGURE 3

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55201  TTTTTAAATT ATTTTTGGTA GAGATGGGGT TTTGCCATAT TTTCCAGGTT
55251  GGTCTCAAAC TCCTGGGCTC AAGCGATCCT CCCACCTTGG CCTCACAAGG
55301  TGCTGGGATT ACAGGCATGA GCCACTATAT CCGGCCAAGA TGTATCTTGT
55351  TGATTGCTCT ACATCAGTTT TTTTCTGAGT CACAGTGTGC CCTTACCACT
55401  TGCAAATTCA AGCCTTCCCT GATTTCAGGA AAGTTGTCTT CTATTGTGTA
55451  TTTACCCTTT TGGTTGTTCT GTTTCTTTTT CTTTTTAGTA TACCCCTTAC
55501  CCCGGTATAG TTTATGTTCC CTTTTTTCTT TGTTATTTGC TATTTTCTCT
55551  GTAATTATTT GCAGCTTTGT TCTTTTTTTT TTTTCCACTT GATTTTTCTC
55601  ACGTTTGTTT TCCATGTCCC ATGCTGCATT GTTTCATTAA ATATTTATTT
55651  GGCATTGTTT TAGTTAGGCA CTGACAGTAA AGCAGAGAAC AAAACAGACA
55701  ATAATCCTTG ACCTCACGAA ACTTATTTAG TGGGAGAATC AGACAACAAA
55751  CAAAATGTAG TAGGCCAGAA GTAATGAATC CAAGAAAAAT AAGGCCATGT
55801  AAGGAAGGTG GGACGAGAAT TGTATTTTTA GAAGGGTGGT CAGAAATGGG
55851  CTTACTGAAA AGTGATATTT GAGCAAAGAC CTAAAGAGAT GCACGTATTT
55901  GGGGAAAAGC ATTTGAGGTA GAGGAATAAG TGTAAGTGGT TTGAGGTGGG
55951  AGCATAGTTC TTAGAAGGAT ACTCATTTCA TCATAGGGCC AGTCCTCTCA
56001  TGACCTCATC CCAACTTAAT CACCTGCCAA AGTCCCCACA TTAAGTGTTT
56051  GGACTTCAAC ATATGAATTA TGAGGGGAAT GCAAACATTC AATCCCATAA
56101  CTGCCATATT TTCTTTGATT AATTTGTTCA TAGTTTTCAT CTGCTTCATG
56151  GTATAAGTTT TATGGCATTT TCTTTATGAC ATTTGGTTAT ACTCTTGCTT
56201  TTCTGTTTTT GTTTTGTTTT GTTTTGTTTT TTCTTGCAAA ATCTTTGAGT
56251  AAGACCTAAC TGGTTCCTTC TTGATTATTG GTCATCTTTG AACTGGAGGT
56301  ATTCGTCTTA GATCAGCTAT TTACCCAAGA ATAAAATTGT GGGAAAGGGG
56351  CCAGAGGAGT GGTTGGGGAA GGCTGACAGC TTGAATTTTC CCAGGTTCCT
56401  TTGGTGGCAT GAATCAGTGA GTAAGAAGCA GAGCTCCTTA TATCACAGGT
56451  TTATTTTGTT TAAATTGATA AACACTGATT CATATTAGAA TCACCTGGGG
56501  AATCCTTACC CATGCCAATG AAATCAAAAT CTGTGAGAGT GGGGCCTAGG
56551  TATATAGGTT TTAAAGTGCC TCAGGTGATT CTCATGTATA TCCAGGCTAG
56601  AATTGCTGAT TTAGCCTTTA CTTTTAGCTA TCCAAGATCA ACTGATGCTT
56651  GGCTACATGC AACCAAATTT CACTTCCGCC TTACCATACT TAAACAGCCT
56701  GCTGCTTGCA AAAAATGGCA GGTGTAGGTG TTCACATTTT CCTTAATATG
56751  TCCCACCTTC TCCCATAGGC CACTCATATT TCCTGACTTT GTCATACCAT
56801  GCAAGGGCTT GTTGGTTTTA TTTTAGGTCA CCTTTTTTAG CGAGCTATGA
56851  ACTGTACCTA CTCTGGCCCA CAGAGGAGTT ATCTGCTATG CCTAGCTTAG
56901  GATGGTTCTA TTTTTTTTGA AAATTTTATT GTGAAATTAT AATATAGAAA
56951  ATGCATAAAA TGTAAATAAA CATCCATGTA ACTATTGCCG AAGTATGGAA
57001  ACAGAATGTT TACCAGGACA CCAAAAGCCT TTTTCATGCC GCTTCTCAGG
57051  CACAAATCTG TTTCTCCCTC TGTAAAGTAA CCACTATCCT GACGTAGCTG
57101  GTAATCAATT CCTTTTCCCC TCATTCTTCT CATTTTCAGG GTAATGGATG
57151  TTTCCTAGTT TCATCAAATG TTTTCCTTGT TTTCAGAAAA GAGAGAAACA
57201  AAAATGCCTT TATTCTTCTA TCTATAACTG GAAGCAGAGG ACTATTGAGA
57251  TTGCCAATTT AAGTTTTTGG TGTTTTTTGG GGTTTTTTTA AACAGATGAA
57301  GTCAGAGATC ATTATAGCTA ATGCCATACT GACTGGCAGT TCAGCATGCA
57351  GTACCCTAGC ACAAACTATT AGCCGGGCTT GATTTATAGT TATCAGTAGT
57401  TCTGAATTTA TGAGACAGGA ATTTTAAACT TCCATTTCTC TTCAAACAAT
57451  ATGGCACTAG ATTTTTCAAT ACAGATGAAG AATACCAACA GTGTATACAT
57501  TAATCACTAT TTTGGGTATC CAAGAATGTA AATATATAAT TAAGTTAATT
57551  AACTTATTTT TTTTTTAGGA ATATGAAGCC ATCTACCTAG CAAAATTAAC
57601  AATACAGATG ATGTCACCAC TCCAGATAGA AAGGTCATTA TCTGTTCATT
57651  CTGGTACCAC AGGTAAGGAT TTTTTTCTTT TTGGAGAAAT TTGGGAAGAA
57701  AGATAATGAA AGGTGGAGAA CTTGCTACAA GTTACACTGA ACAATTTAAA
57751  TTGTTTAGAA AACTTGTTAA ACTATTGAGC TAATTCCAGA AGGATTCATT
57801  TTATAATGAA TAAATGTGTA CTATAATAAG CTTAAGTCTT TCAAGTAGTA
57851  GTACATCCGT GTTGTAAAGA TTAAAATAAT ACGAATCTGG AGAAGGGGCC
57901  CTAAACACGC TTAGGTGATC TTATTAAAAG TAGAGGGCGG TTAATACAGC
57951  GTGTAGCATG GCTAATGTGA GCTTCTTTCT CTTGCCATCA ATATTTCCAT
58001  CCTTTCCTCC CTCTGTTGCT ATTTCAGAAG TACCCTAAGC CCCTTATTTT
58051  CAAAGTTAAT CCAAGCATGC TCTTAAAATC TTCCTTTCCC AAGACCTTGC
58101  TACCTGTGTT TATCACCTTT GTTTCTCTCC CAACAAAGCA CACAAGGCAT
58151  TTTTACTTTA TTTCCAGTTT TTCCTACCCT GCAGTTCACT TCAATCTTTG
58201  AACCAACAGT TATATAAGGT AGTAAGAACA GCTTATATAC TTAGCACTGA
58251  CCTGGAAATT GAGGACAGGT GATCTGATCC ACAAGTATAG AACTCTTTGC
58301  ACTCTACTGC ACTGCCCATA GTGAGTAATA TGACTGTATA TTCATCCCCA
58351  AGGCTCAACT TCCTAATTGT CATTGACTTT TTCATTTCCT TTGCCACATC
58401  TGTCTAATAA TTGCTCTCCA CATCCTATAG GGTCCGTTTT GTCAGTATTG
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FIGURE 3

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58451  TTAACATTCC TTCCTTTTTT TAATAGTGAC CTTAATCTAG TTCAGGTCCG
58501  GATTTGCCTC CTTTCCAAAC TCTTGTTATT TGGTCTGTTC TGTACATTGT
58551  GGCCAGACTT ATTCCCATGA AAGATATTTC TAATATTGAT ATTTTTCCTT
58601  TGCCAAAGCC TCCTTTGGCT TCATTCCTAC AAAAGTTTAT AGAATGCCAT
58651  ATGCCCTTCT GATTTTTTGG TTTCTTTCTC TCATTGTTCT TCTTTATGTC
58701  TGCATTTCAG AAAACAACTG CTGATGGTTT CCTGTGTGTG TCTTCTTTTC
58751  CCCACCTAAA ATGCATCACA TTTAGTCTCC CTATTCTTGG TTCATATGTC
58801  ATCTCCTCAG GAAGACATGA TGATTAATGC ACTCTTCCTC TAACCCCTAG
58851  TCATTTGGAG TTCCCATAGA AGCACAGCAC TTCATCTGAA ACTTAATCAC
58901  AGTATCTGGG TTTAGCCTGA GGGCTAGGAT ATTTTATCTC ATTCAATTGT
58951  ATTGATACTA TATTTTTATC TTTATGAATT TTATAGTGAA ACATTCTTCA
59001  ATTAGAATAT GCCCTCTGAA TTAACATTAT TATTACCATG ATATAACAGT
59051  CCTGTAGGGC ATAAGTTTAA GGTCATGCCA TTGTTAGGCA AAAAACACAG
59101  CAGACCCTCT GCTGGTTTAA CTGTTCCCTA AAGTTTTCCT CCATTGAGAG
59151  TCTAATTTCT TGATTATAAC TTTTGGGGAT ACAGAGATAG CTTTGATTCT
59201  ATGTGGGAGA TTTCTGTACT AGCAGATGCT GGTATGAAGA ATAGATAAAA
59251  GAAAATCTCT TTATATGCTA CATGCCTTCC TTTCTCCCAA CCTAGACTTC
59301  GATAGCTTGA GTGGAAAAAT ATTTTCAGCT GCTCTTCATA ACAGCCTCTG
59351  TGAAAGCAAA AAGATTATCT ACAAAAAATT ATACAAATAC AAGATTAATT
59401  TCCTAAATTT TATGCCCTAA GTCACATGTT TATGGTGCCT AAAAAACAAT
59451  TAACTTGATA ACTAAACATT TATGTATTAT CTCTTGAAAA GGTCTATTTT
59501  CACACTATTT CAAAAATTAT TTATTTTATA TGCAATACCT AAGACATAAT
59551  ACTTGAGAAG GAAAATATAT CCTGTCATGA AGATTAAAAA GTTATAATAT
59601  TTAGGTAATT TATCACAAAG GAATTTACTA AATTTTGCTA TATCAGTTGT
59651  GGAATTTTCA TAGTGTATAC ATGATCACTT AATAACAAAA TTTTACTTGC
59701  TGTAACCTTT TAACATGAAT TTATTTTAGT GCCCTTTTAA TCTTCATGCA
59751  ATAACTTTTA GGCAGTTTGA AGAGAACACA TGAAGAAGAG GATGATTTTG
59801  GAACCATGCA AGTGGCGACT GCACAGAATG GCTGACTTGA AGAGCAACAT
59851  CATAGAGTGT GAATTTCTAT TTGGGAAGGA GAAAATACAA GAGAAAATTA
59901  TAATGTAAAA TGGTAAAAAC ATAAGTAGTT TTTTTTCAA TTACATGTTG
59951  CTTCCAGACA TACTTCTCTG CAACTTGTTG AGCAACATTT TAAGATGTTG
60001  GACTTCTGCA ATAGATGACA CTGATGGTTT TACTCCTTTT TTTAAAAACA
60051  CATGCGCGCG CACACACACA TGCTTTACAA GTTTTATTAT AAACCAAGAA
60101  TTTTGGACTT GCAAAGAGGT ATTATTGCAA TAATGCACTT TTCATACTTG
60151  AAATTTATTT GTATGATATA AAGTTATTAC TTTAAACAAA ATGCAAGTAT
60201  GGGGGGATTG TTTATAAAGT TTGGGTAATT TATAACAAAA TTTGCTAAGG
60251  TTTGCTAAAA ATTCATTTTT CTGTTCTATA TATTACATTT TTAACATAAT
60301  TTTACAGTTC AATTTTATGA TGGAGCCTCT TACAGAAACA TTAACAAAAT
60351  GCAGGAATCT GCCACATTTC TTTTTTAGTA TAACTTAATA GCTTAATTAC
60401  CATTTTATTT TTTATACTTC TTCCATTATT AATCTTTAAA TCATGATCCT
60451  AATTAGCTGT CCTTACTTTA ACTTGATCTA ATTATTGCTT CCTTTCTTAT
60501  TACTTTCCTA ATTTTTCTAT ATTTTAAAAA CTACAGTTTC CATGATAAAA
60551  GGAAAACGTT TTGATTTATA GTACCAAGTG CTTAAACACA AGGATAGTGT
60601  TAGATTTTCG AGTGACTTTC CTTTTTGCAT TTTTTGGCAG TAAAAGCCAA
60651  ACGTTGTATT TGTTCTTTTC AGAGTTGTCC AGCCCTTTTT TCCTTTGTCC
60701  AAAATGATTC TAAATAGAAT CTAATAAACC AATGTAGCAT TATTTTTTTC
60751  TAAATGAAGC CCCAAAAAAG AAAAGTGCCT TGCATCATTT AAAAAAAATA
60801  ATTAAATCCT CATGGCCTCT AAATTAGTAT GTAGAACACT GAAAAGTTCT
60851  TAACATTTTT GTGTAATTTC CTTTCTTTTT AAACCATAAA TTAGTTTAAA
60901  CTGAAAGTAC GAGGCTGGAA GAAATATTAG TAAATTATTT GGAATATAGA
60951  ATGTTTACTC TTTCTTTTTA TGTTGTCTTA ATGATTCTGT GAGATTGTTC
61001  CGGCTCAAAC AGAAGCTTTT CTTTGGGGAA GGTGATTTGT GGGAGACTCT
61051  AGTGTATTTT AAATTAGCAT TTTAATCCAT TCTTGACATT CAGTTAGTCC
61101  AGATCTGCCC CATAATTTGC TTTAGTAAAG TCACTTTATG GATTTTTGGC
61151  TATGTTTTAG TTTGTGTGTA TAAAAGTTCT AAGAAAACAT TTTTGCTATT
61201  TTAAGTATGT AAGGGAAGAG AGGAGTGTTT TTAACTTTTT ATAGTTGATG
61251  ACTTTAGGGG TAGCACAAAC AAAACTCCTT TGTATCTAAC TTTTCTCAAT
61301  CCTCTCTTGA GGTGCTTTAC TAATGGGAAT GATTTCTGTA TGTTCCCTTG
61351  GTACCCAAGA GGTACTATGC AAAGTAACCT ATTACACCAA GTTACTTGCT
61401  TTGCTTTCCT CTCTATGATG TGATAATACA GTAAAAGCTT TCTTACCCAG
61451  CATAGTGGGA GAGTGGAGAT TAATTAAAAT TGTTAATTAA GAGTTAATTC
61501  CTATTGACCC AGGTGATATT TCTCTTCTGA TTTCCCTCCC CTTCCCTTCT
61551  CTTATCTTAC CACTGTGAAA ACAGCATATT GTTAATCTCG TTGTCGTCCA
61601  GTATTCTGCT TTGTGATTAG GTCTTTTGAT GTACAGTGGT CTAGTGGAGT
61651  CAAGATTCGC ATTGGGTTTT CTAAAATTCC AGTTGATAAA AGTTCCAGAT
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FIGURE 3

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61701  AACACAGCTT TCCTGTATAT AGATCACTAT TGGGCAGGTC AGCAAAGATC
61751  TCTTACAGTG TAATAATAAT CTATGATGCT TCATTTAGCA GAAACTCTGC
61801  TTAAAAGAAT CTTCATAATA GTAAGTTTAG GTTTTAAAAA CTTGTTTCAT
61851  AAATATACAT ATATCCTCTC TAGTAGTCTG GCCAAAAGAA CAGATTTTGT
61901  TATTGATAAT TTGTAGCTGG TAATTTTCCA CATTTTCTAT CCACTGTAAT
61951  TTTTATGTTG TCACTGAAGT GCCTGCCCAG TACTGTATAT TACAGTCTCT
62001  CACAAACACT GGGAAAAGGG ACTGTCATCA TCTTGAGTAC TCTGTGTGTA
62051  TATATATATA TATAGATAGA TAGATTTTTT TTTTTTTTTT GAGACAGAGT
62101  CTCTAATGTC ACCCAGGCTG GAGTACAGTG GCACAATCTT GGCTCACTGC
62151  AACCTCCACC TCCTGGGTTC AAGTGATTTT CCTGCCTCAG CCTCCCAAGT
62201  AGCTGGGGTT AGAGGCACAT GCCACCATGC CTGGCTAATT TTTGTAGTTT
62251  TAGTAGAGAT GGGGTTTCAC CATGTTGGCC AGGCTGGTCT CAAACTCCTG
62301  ACCTCAAGTG ATCCACCCAC CTCGGCCTCC CAAAGTGCTG GGATTACAGG
62351  CGTGAGCCAC TGCGCCTGGC TGAGTACAAT ATTAATGTAG ACAAACCATG
62401  AAGTTTATTA TTTCATATAA GAACATTACA GGTTTGTTTT TTCTTGCATG
62451  TCTGTCCACC TAATGTTTAA GTAGTTCTGG TAGCTCTTCC TATTCTTTAT
62501  TCTATTTGAT TCCATTTCTG TGATTCTTTT ATTACCACTG ATGTTTTGTG
62551  ATAGTTAACT ATGATAAATT TAACTGATCA TGATTTATCT TCTAGAGTAT
62601  TTAAATAATG TATGAGTGAC CACCCAATTC CAACATTAAA AGTGTAATCT
62651  GGGCCCATAA TTTATAGTGA AATTGTATCA AAACATAGGG AAACTGTATT
62701  ACTGTCCATT TTGAAAATAT GAAACTTGAG TATTGAAAAT ATTCAAACAT
62751  GGAATGGCAG TATTCTAATT TCAGTTAGTT GGTTCATGTT AATTTCTTAC
62801  CTGTTAGATG TTTAAACTGC AGTGACCTTT ACTTGTATCT ACTCTGTGGT
62851  GGAAATGTTA AACCATGATA GCTTTTGCTA CCAACTCAAC CACTTAACTT
62901  TTAGAGCAGT TTTGGGGAGA GTTTATGCTT CATCTGAGTT TAGAAGTAAT
62951  GTCAGAAAAT GTTAAGCATG TCTGTATTAA GAAAATATAA GGTTTCTAAT
63001  TGTCTTATTA ATATGGTAAT TCAAGTGAAT TAGAAATATT TAACTGCAAT
63051  CTTGAATTAT AAAGTTGAGA TATATATATA TATGTATCAA GATCTCAACT
63101  TGATGTAAAG TAAATGAGCA GTTACCTGGC GGATTTTTTT TTTTTTAAAT
63151  AACTGATTTA ATCCATAATC CCATAACAAA CATAGCTTCA CCTCAGTATT
63201  TTCTTTCTTT CTTTGTTCAA CAGTGCTCCG ATAAGGGAAT GCTAGAAAAT
63251  AGATGAGAAG TACTGAAAGA CCTTTTTTTT TAATTGATTA GAAAAGTAAG
63301  TCTCTAGGGT CTTTGAATGC TGGAATTTTT TTTTTTTTTT TTGTCTTTCC
63351  CATCTGTGGC AGCTAAAACA AAAATCACTC AAAATATTCA GGTTTACATG
63401  TTAGCTCTCT CTCATAGGGA GCTGCCATAC CTCACAGTTC AAAGTGTATT
63451  CTATAGATCA GTAACATTAT ACTGACATGT AATTGCAATT TACTATGCAG
63501  CAAAAATGAT TCAAGAAGAA AAATAACCTA CAGTGTCTGT ATACCTTTGT
63551  ATACACAATT GCTTAAGTTA CTCTGCTTTT AACATTTGTA CTTGGATAAA
63601  ATGCTTATGT CTGTATAGGA ATGTCACAGT GCAAGATGCT GCTAGCCCAG
63651  GCACAAAGTA TTAAAATTAT TTTGTGAAGA TTGGTGGTTG TATTAAAACT
63701  GCTGTGCCAT TATACCTCCA AAATATTGAA AAGCTCATTC ATACTGCTGC
63751  TTATACCTCA AAACTTCTTT ACTTAGATTG TTATCTGCTG GGTAAAAGTA
63801  ACCCAAATTT ACTCTGAGTT AAGAAGAGTG GATGAACATT GAATGTTGAG
63851  AAGCACTTAA GAGTATACTC TAAAACACTG TGGTTACACA CACACACAAA
63901  ATTATGGTCT GTAGTCCAGG CAAGCCTCAA ATTCCAGCTC AAGTTTATTT
63951  TTAAGGATTA GTTGAGCAAG TTTGGAGTTG GAAGTGAGAG AATCGTGTTT
64001  AAAGGAAAGG GTAGGTCATC CACAGAACAG CTTTCAGTCA TTACAAAAAA
64051  AAAATACTTC TTGCTTTTAT ATTACCATCT TCCCCCATTA GGCCTACCTG
64101  CATACTGTGC TTCATCAAAT CTAAGATCAC CTCACAACTA TACCATTATT
64151  TTAGGCACCA CTAAAAGACA GTGTATTGCT AACAAAACTA TGATAAACCA
64201  TTGATAATAT ATCCAGATTT CAGAGATGTT ACAGTGCATC TTAGTTGATG
64251  AAACAAAAAT ATACAAAACA TGAGACACAG TAAAAATGAT AAGTACCACC
64301  TCATTATACC TTTTCACAAG CAAATAGTGG CCAAAGATGT GAACGGCCAG
64351  ACACGGTAGC CGACATATGT AATCCCAGAT ACTCTGGAGG CTGAGGCAGA
64401  GGATCACTTG AGCTCAGGAG TTTGAGACCG GCTTGGGCAA TATAGTAAGA
64451  CCCCACAGAA AAATGTAAAG CCAGGTGTGA TGGCACACAC CTGTAGTTCC
64501  AGCTACTGGG GAGGCTGAGG CAGGAGGGAT GGCTTGAACC CAGGAACTGG
64551  AGGATGCAGT GAGCTATGAT CACACCACTG GACTCCAGCC TGGGTGATGG
64601  AGTGGGACAG TGTCTCTTTA AAAAATGTGG GCCAGGTGCA GTGGCTCGCA
64651  CCTGTCATCC AAGCACTTTG GGAGGCTGAG GTGGGAGGAT CACTTGAGCC
64701  TAGGAGTTAA GAGACCAGCC TGGGCAACAT AGACTCCACA CAAAAAATTT
64751  TTTTAATTAG CTGGGTGTGG TGGCATGCAC CTATAGTCCC AGCCACATGG
64801  GAGGCTGAGG TGGAAGGATC ATTTGAGCCC AGGAGATTGA AGCGGCAGTG
64851  TGTGGTGATT GTGCCCCTGC GCTCTAGCCT GGGCAACAGC GAGACCTTGT
64901  CTCAACAACA ACAACAACAA AAGGCTATCT ATTGTGGGTA CACTGCCTAT
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FIGURE 3

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64951  GGGGTAGTCC TGCTCCACAA GGAGCAGTTT TTAAAAAAAA AAAGTTTAAG
65001  AAGTGTTTTA TGTAGCACTT TTTTCATATT TACATTTACT CACCATATGG
65051  CTTCAAAAAT CATAAACATA CTCAACTAAA ATTACAGATC ACCATTGTCC
65101  TCAATGACAC AATTTTTGTA TGGTGTACCT TACCTGTAAT TCTATTTCCT
65151  ATGGGAGGAT TTAAGAGATA TCTTAGGAAC ACTATTTAAA GGGATTTACT
65201  GAAGTGCCAA CCTTGTGAAT GATTTTACCT CAAATTGTTC AGTGGTAAGA
65251  AAGGTAATAA AGCATTTAGT TGTGCCTTTA AGTAGGCTAA TTTTTTTTGT
65301  TTTGTTTTGA GATGGAGTCT CTCTCTGTCG CCAGGCTGGA GTGCAGTGGT
65351  GTGATCTCAG CTCACTGCAA CCTTTGCCTC CCGGGTTCAA GCGATTCTCT
65401  CGCCTCAGCT TCCTGAGTAG CTGGGATTAC AGGCGCATGC CACCACGTCT
65451  GGCTAATTTT TCTTTTTTTT AGTAGAGACA GGGTTTCACC ATTTTGGTCA
65501  GGCTGGTCTC AAACTCCTGA CCTTGTGATC TGCCCACCTC AGCCTCCCAA
65551  AGTGCTGGGA TTACAGGCGT GAGCCACTGC ACCCGGCCTT ACCAGGCTAA
65601  TTTTTAAAAA CATGCGTTTT TAATTACCAG GATTTACCTG ATAAAACTAC
65651  TCTTTGTCAA GGTTGTAGGA CTTCTGAAAA GACAGAACTA GCTTTGTTGC
65701  GTTTCACGAA GGACAGATCA GTTCGTCTGT ATAGGCTATA AGCAGGTAAG
65751  TAGTGCACTC TATTGGTGAA GGATTTCTGT TGTTTTGGAA AGCCAACTAT
65801  AGCTGGCTGC ATGGAGGGAA ATCCAAAATC CAGATGACGT GGTGTGAGTC
65851  AATGGGATGA GAAACACTGG TATTTTCTTT ACAATTTCAT TTTACAAAGA
65901  GCACATTAAA CTAAAATTTT ATGAATTATG ACTTAATCTA ATAGTTCAAC
65951  AGCAGACTCA AGAAAAGCAC AGATGTGATT CTAACAGAAG ACTACTCATA
66001  TAAACAGGTT TAATGCAACA TGGAATGCAA AAGATTAGAA CCATTAAAAT
66051  ATTTAATTCT TCAACTTTAA AAAATTAAAT AAAATCAAAA TAGGATAATG
66101  ACCAGAATAG TGCCATTATA ATCACATCAA AAAGCTTCCA TTAACATTTT
66151  ATGAATTTGG CAATCTAGTA CAATACATTA AGTATTGTGT TTCACTCAAT
66201  TTTGTGATAC TCCATTTTTG AAAAAACTTA GAGGCTTCAG ATACCCATGA
66251  AAAGAAAAAA ATCAGGGTAG AAACACATAG GCTGAGGTTT GCTAATTCAC
66301  TGTTTACAGA GGACCTTAGA TGTCCCACTA TAATTGCTCT TAGGTATTTT
66351  TAACAAATGA ATAGTCATAA TTCACAGAAA AGACAAGTGG TACTTTTTAT
66401  CTACATAGAC TATACTATAT AAACTTTCAG TAAAACATTT AAATTGTTTT
66451  ACTTTTAATC TTGTCAAGTA ATTTTCATTT CTTCTACTTC AAAAGGTTGA
66501  CCAGGTTGTT TGCCTGTATT GGGATCAACG AATGTTGGAC TATACTATGT
66551  TTAGTTATAA TAACTAATTT ATCCACCCTG ACTTAATATG TGGGAAACAA
66601  TACACCCCTA AGTGTATTGA GATGTTTCTT TGAAACAAAA ATATTTAATT
66651  TTATGCATGT GATAAACAGC CTTATTCAAT GTATACTTTT TTTAAATGAG
66701  CAACACAGAT AGCAGACATA TAACTCCTTA TTACCCATAC TCTTGACTAC
66751  CAAGAAAGGA AGCCAAACTT TTAGAAAAAT ACAATGCAAG AAAAGATTCA
66801  AGTTAAAAAT ATATTCCTTT GGTTAAAAAT CATCCCCTTT ATAATATTCA
66851  TTTGTAATCT AAATTCACAG CATGTCCCAC CAGCCCAAAG TAATCTTCTA
66901  AATGTCATTA TACTTGTAGT ATTACAATGT TTTTTCAGTC CAGTATTTAT
66951  GGAGGTCACT CGGCTGCAGC AACAAAATAT TTCAACTCTA GGAAGAGTGT
67001  AGCCTTGTAG CATTAGCCCC TTTGACAATT TTCTTACAAG ATTTTTACTT
67051  TAGAAACCTC CGACACATGT AGTTTTCTTC AGATACAGTA TATCCAAACT
67101  TTTTATAGAA ACCAACATTT TGTGGTAGAC ATTCAAGGGT AATCTTGTAA
67151  CAGTTCAGTT TCTTGCTTAG CAAAGTAAGG GTTGATAATA ACCTGAAATT
67201  TAAAAAGGGG GTAGGGTGAG GAGATAGCAT TTATTAATAA AAATTGATTC
67251  TAGTAACAAT ATGAATTAAT GTTATAAAAC TTAAGTTTCC TTAGAAACAG
67301  GTTTAGATTA TGGCTTTTCC CACTGCATTC ATGTAAGTTG ATAAGCATTT
67351  AAATCACCAA AGCATTTTTA CTTAGAGTCA AATATACTTT TATCTAGTAA
67401  TCTCCAGCTC ACTAATAAAC AGGACAAATA CAAAACTCAC CCTAAGCCCT
67451  CTTTAAAAAT GAAATTTAAG GCTAGGTGCA GTGACTCATA CCTGTAATCC
67501  TAGCACTCTG GGAAGCCGAG GCAGGCGATC GCTAGAGCCC AGGGGTTTGA
67551  CACCAGCCTG GGAAACACGG CAAAACCCCA TCTCTACAAA ATATAAAAAT
67601  TAGTAGGGCA TGATGGCACA TGCCTAAAGT CGCAGCTACT CCAGAGGCTG
67651  AGGGGGGAAG ATCACCTGAG CCCAGAGAGG TCAAGGCTGC GGTGAGTAGT
67701  GATTGTGCCA CTGCACTCCA GCCTGGGCAA CAGAGTGAGT CTCTGTCTTG
67751  AAAAAGAAAA ACGAATTTTA AGATGCATGT TAACACTAAA AACTCAACCT
67801  TTAAAAAAAA AAATGACCAA AATTATTTTG TAAAAATTCT TTATTTAAAT
67851  CTATTTAAAC AACTTCGGAG CAGTCGACAT ACCCACATAA AATGAGTACA
67901  TAATAGCTTT GCTCTTTAAT CATTTTTAAA GCTACTTTAA TATTTGTGAA
67951  GGTGTGTATC AGATTAACTC AAGATTGGTC TAATTAATAT GAAGTGGAAA
68001  CAAAGCAAGT CTACATCTAT ACAAAATTTC TTAATGAATC CAAACCCAGT
68051  ATTAAAGTGT GGATCTAAGT GCCTTAGAGG ATAAAAACTA TAAAAGATAT
68101  ACAAACTTGA AGGGTCTGCC CATGTTTGAA CAGACTAAAA AATCCTATTT
68151  TTAAAAAAAA CAAAAGACCT TGACTGAAGT ATGCCTGGCT GGTTGCAGTG
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FIGURE 3

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68201  GCTCATGCCT GTAATTCCAG CACTTTAGGA GGCCAAGGAT CACTTGAGTC
68251  CAGAAGTTCG AGACTAGCCA AAGCAACATA GCAAAACCCT ATCTCTATAA
68301  AAAATTAGCT GGGTGCAGCG GCATGCACCT GTAGTCCCAG CTACTTGGGA
68351  GGCTGAGGCG AGAGGCTCAC TTGAGCCCCA GAAATTCAAG GCTGCAGTGA
68401  GCTGTGATCG TACCACTGTA TACTCCAGCC TGGGCAACAG AAAGAGATCC
68451  CATCTCTTAA AAAAAAAAAA AAAAAAAAAA AAAAACATAA ATTATATAGA
68501  CTAGAACACA AGAAATCGGT CTGTTTTGTT CACTGAGGTA TTCCAAATAC
68551  CTAGAATAGC ATCTGGTACA TAAGCAGGTA TTTAATATTT GTTAATTCCT
68601  TAAAACTCAG AAGAGTTAGT GTTAAAAAGC AAGTTCTTGG GCCAGGCACA
68651  GTGGCTCCCA CCTGTAATCC CAGCACTTTG GGAGGCCAAG GCAGGAGCAC
68701  TGTTTGAGAC CAGCCTGAGC AACATGATGA GGCCCCATCT CTACAAATTT
68751  TTAAAAATTA GCCAGGTGTG GCGTGTACCT GTAGTCCCAG CTAATTGGGG
68801  GGCTGAAGAG GATTGCTTGA GCCCAGGAGG CTGAGGCTGC AGTGAGCTGA
68851  GATTGAGCCA CTGCACCTCA GCCTGGGTGA CAGAGCTGTC AAAAACAGAC
68901  CCTGTCTCAA AAACTAAAAA TTATAATAAA TAAGAACTAC AAGTTCTTAT
68951  AAAATGGCAA TAAATCAATA CCACTTATTT ATATTTATTT TAAATGATTT
69001  AGATATATAC AGTGAAGGCT GTTTCAGTAT GTATTTCTAC AACTTATGAG
69051  AATGAGAGAT CACAGAATAT TCTGTAATAG TTGAACATTT CCTTTGTTTT
69101  TAAATATGAC AGAGAAGCTG AGGCAAATCC GATTAGCCCA AAAGTTTATC
69151  TCCTACTAGG ACGAGAGCAT TACTATAAAA AGTTAGTAAT TTAAAGATGT
69201  TACTGTCTGT AAAGAAGTAT GCTTCCAATT TTCAAACTTT AAGGCAAAAT
69251  ATGTATAATA ATACTTTATT TCTTCATGAA ATTCAGTCTA AACTATTAGA
69301  GTGAGAATAA GTTCAGAATT AATGAAGCCA AAAAGAACTT CAAACAAGTA
69351  TCTTGTTAAG AAACTAAATT GGAACAAAAT TTATCCAGGG TTACCTTGTT
69401  TCTGCCTACT TACAATTTGC CAAGCTGCTT TCCTCTGCAT TCATCACTAA
69451  CAACAACATC TTCTACTCTT CCTCTCTGAA AATATTTACA ATGTTTAAAG
69501  GAGTAAGCAT TTACTTTTGT TTTTAGCTAA AACGAGTTGG TAAGAATTTA
69551  CTGATAATAA GTAGTATATT TTGTAAACTT GAACTTAACA GAAATCAAAT
69601  GCAAAAAATA TTATACAGTG AAGGCTGTTT CAGTATGTAT TTCTACAACT
69651  TATGAGAAGG AGAGATCATA GAATATTCTG TAATAGCTGA ACATTTCCTT
69701  TGTTTTTAAA TATGACAGAG AAGCTGGGGC AAATCTGATT AGCCCAAAAG
69751  TTTGTTTCCT ACTAGTATGA GAGTACTACT ATTAAAAGTT AATAATTTAA
69801  AGATGTTTTT ACTTATTAGA GGAAATAGTA TGAGTCAAGT TGTGACCTAA
69851  ACTTGTTTTG GCTATGTCCC CAACCTTCCC ACCCCATTGT CTTTAAACAA
69901  ATATCAGGAT CAACATCACC AAAATGTAAC CTTTTCATGA ATATATCCAT
69951  CATTCTACTC CTTGCTTACT AGCAAGTTAT TTTAGATATC CAAATAAAAT
70001  TAATGTCTAG TACAGAAACC CCACCGAAAT TCCTAAGTGT GACAGAACAC
70051  ATCCCAAGTG TTCCTACCTT ATTCTCATTG AATTAAGGTT TTCTCTCCCT
70101  CTTTTTTTAT TTACTATTTT ATGTGAGTTA TTGAGGGATG AAAGGGCACT
70151  ACATGCATTA GATGTATCAT AATTAGAACG GAATAATCTG AACCCTTTAC
70201  CATGTGGAAA CAAATTTATG CTAACGTGGT ATATTCAGAG TTGTTTTTTT
70251  TAAAAGAGTA ACATTAGGGA TTTTGTGCAT TACTGCTAAG TTGTTTGGTT
70301  TCTCTATGCC TATACCAAAT TGATCCACCT TACAGAACAA TTTTAGCATA
70351  CAATTCATAC TGTTATACAT TTTCTTTCTT AAAGCTCTCA GAACACACTG
70401  GGAAAAGGGA TTTCTAAGAG GCACTGAAAA TCAATGAGAA AACAGATTTG
70451  TCTAATGGAA ACTCAAAGTC AGTTGTGCTA GAAAACAGCT GTCCATTTTA
70501  TTTATAAGCA GCACATACCT TAGCACAGGA ATGGATGAAT TTATGTTCTA
70551  TAATCAGAGT TGCCGTAGCA ACAATCTGTC CTAGAGTCAC ATCTTCTACA
70601  ACTGTAACAT AATAATCCCC AGATTTCTTC ATATGCTCAA AAGATTCTGT
70651  GGAAATTGGA TAACAAAGTG TTACATAGTA GACATTCAAT TTTATGGGGA
70701  GCCAGAAAAA TATTAGGATT AGCTGACTTA ATTACTAAAT GTTTAAAGCT
70751  GTTTTACCAT AGTAATTTAC CTTCCATTTC TAAAGAAAAT ATTACCAAGT
70801  AGTTGAAATA TCAGCAATTA GTATCAATTG GAATATAACC TACACATTCA
70851  AAATATCTGC TAGCAAAATA AAGACTAATA TAGCTATTTT AGATGAACAA
70901  CACTTAAAAT ACAAGTAAAT GGCTGATGTT GCCACTTCCA TGACTAATGA
70951  AAACTTCAAT TTCTTCATTT ACTTTAAATA GATCTCTTTA ACTTTTATAC
71001  TCAATAGATA TTCAAATATA ACCTTTGCAC ATTTTAACAA GAGCATGTTT
71051  ACATGGCTCA ATTCTAGAAT TTTTAGTCTT TTGCTTTCAA AATATTTTTA
71101  CAAAATATAT TTTAATTTTC CCTTTGTGAT GGAAAGTGTT TTGTGATAAC
71151  ATGACTTGCT CTTGTTTGCT TTGAGAGCAC CTTGCAAGGA AGTAAAAACA
71201  TATCTGTTTC CAAGTAACTT TTCCAAGTCA CATAGCAAAT AGGTGCAAAG
71251  ATACTTCCCC TCAAATGGAT TTTCAGTACT ATTGCTGAAA TAACATGGTT
71301  TCTCATCTAA TTCATGTGCA TGCAAAGAAA AAATTCAGGA ATAAAAATTG
71351  AGGCTAATAG TCTCTCATAT TGGTAATTTC CTATGGGGCC TCATTCCAGA
71401  TAGAGATCTA AAATGGGAAA AAGAAATTCA GTGAATGAAA ATAAACAATG
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FIGURE 3

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71451  AGTAATCAGT AATGATGGTC CTCATTCTCA GGAGGGTCAA ATAGCAATTC
71501  AATACAAAAT TCCCTATTAT AAGGAAATGA AGAATTGTAA TTCCTCAGCT
71551  ATTAAATATT ACTAAATATT TAGTAATGAT AATAATACTT CATTTCCTTT
71601  ATAACAGGAA AAAGCAGTGG TAGAGCACTG GACAGAATTA AGGTTTTATT
71651  CCTCACCGTA GCAATAACTA CCTGTGATCT TGGGCAAGTC TTTGGATCTC
71701  TCTAAATTCC TATTTTCTCC TATGTCTAAA AGAAGAGGGG CAGGGGACGG
71751  GTGGACTAAC TCTTAAGATG CCTGCTAACC TTAAACTTCA ATACAAATAA
71801  ACCCCAAAAT AAATTTAAAG CGTATAGTCT TGCTTTTTTG ATTTGGTAAT
71851  GAAATTTCTG TAAATAACCA CAGTAAGGGA AATACTACAA TAAAAAAACG
71901  AAAAACCTCT AGAGCTAACA CCTAGGTCCT ATGGTACAAT AATTATCTAA
71951  TAAAGTAGTC AGATAGTTTG CAAAAACAAA GTTACTGGTA CATTTGGATT
72001  CTAGAACAAC TCAGCCACAT TAAACATTTG TATAAAACAG CTAATTTGTT
72051  CTTTGAATAA TTTCCAGCTA TTTGAACAAA AACAGAAGTG GGCACTGAAC
72101  AGCTCTAAAC AAAAATGAAA TCATGTTTCC CTTTATTTCA GGAAAAAGAG
72151  GTTATAGTAC TTACTCATAA ATTGTTCAGG GCTGACAACT CCAGTCTCTG
72201  TTAGCTGACC CAATACCTTA AAAAAACCTA GTTTTGAAAA ACAGATTTCA
72251  AATTACGAGA ATAGCAAAAG GAAGACAGTA TGAAAATAAG CAATATATTA
72301  AGCAGGTGGG CTTACAGGCA ATTATTTTTT CAGAACTTTC TATAATCTTT
72351  TAATTATTAG AATAAAGTGA ACCCTATTCT TCTATAATCA CTACATATAA
72401  CAAAAATAAC AGGTTTTACC AGTGCTTCTG CCTGCATAAG ATGTTTTAAA
72451  TAGTGCTGAC CTTAATATCC AGTATTTATA GACCCAGAAC ATACATTCTT
72501  CAATGTATTA TATTTTACAT TAAGTTCAAT GCAAAGGGTG CCAGATTTTC
72551  CCAAATATGT GATTTGGTTT TACTTAAAGG TGCAACATGG CTAAATACAA
72601  TATTCGTAAA TTAAAGTATA AGTAACACTG TTGAGATTAC ACTCTTTAAA
72651  ATTGTAATTT CTAGTGAATT TCATTAGTGT TACCGGAAAT TGATGTGAAC
72701  AGTGCACCTG GAATTTTGAA AATCTTAACT TTCCTACACT CAATAATTAG
72751  GCCAAAATTA GGCCCTTCAG GCTGTCTAGC AAAGAGATAA TTGTGAAAAG
72801  GACAAAGTTG ACTTTTAATT ACCAAAGTTT AAGGAAGTTA ACTTGGAGAA
72851  TTTAGATGTT AAAAAAGAAA TAACTGTATA AAAACCCTTT CAATTTATCC
72901  AAGGAAAATT ATTTCCACCT TCATTCCCCA ACCAGCTTCT TAAGATCCCT
72951  CCTTATGTGT CATCATACAT GATAATTTAA TTTTTGTTTA TGAGAAATCT
73001  TTTTGGCTTA ATTAGGAAGG AGTGATGTTG TATTTAAGTC ATTTTAAATA
73051  TTTCACAGTA ATATTTGGTC TTAGCCATGA CACACACTCA TTGGTATTGA
73101  GTGTCCATCA CTTTAAAAAC TAAGTATTAT ACAAAAAATA GTCCAAAAGT
73151  CAAATATTTA AAAAAAATTA TCTGCATCAT AATGTTTAGA GAAAAATGGA
73201  AGGCTAACTC TAATTTTACA CAGGATTTTG TACATTACCT CTATTTAAGT
73251  CAGCAGTACA AAGAGGCCTC AAAACCAAGC CTTCTCCAGG ATGTGTTGGG
73301  GAAATGGCTG GAGAAAATGT AGCTGTATTC TGACTCCAGT CCACTTCTTT
73351  GAGTAGACTT GGGTCAAACA TAGGAGTTTC ATCAGGTTTC ATTTTTCTAG
73401  TAAGGTCTAA AATAAAAATT TGAATATTAA GTCACTTTAT TTAATAGAAG
73451  GAAAATTATG ATTGTTGAGA AAGTTAATAT AAATTAATGC AATTAGAAGC
73501  ATTCTTTAGC ACATATGCGA GATATTTTAC TGCAACCCAG CCTGAATCTA
73551  ACATTAAATT CCACAACTAC AGATAAATAG AAAAATCATG CCTACTATCA
73601  GATAAAAAAA TGGCTAAGTG ACTAAATTAG TAAGTTTTAA ACTATAAAAT
73651  CCCATTTATT ATCAAGTCTT TTTTTTTTTT TTTTTTCAG ACAGTCTCAC
73701  TCTGTTGCCC AGGCTGGAGT GCAGAGGCGT GATCCCGGCT CACTGCAACC
73751  TCTGCCTTCT GGGTTCAAGT GATTCTCCTC TTTCAGCCTC CTGAGTATCT
73801  GGGATTATAG GCACGTGACA CCACGCCCGG CTAATTTTTT TGTATTTTTA
73851  ATAGAGACGG GATTTCGCCG TGTTAGCCAG GCTGGTCTCA AACTCCCGAC
73901  CTCAGGTGAT CTGCCCGCCT CGGCCTCCCA AAGTGCTGGG ATTACAGGCG
73951  TGAGCCACTG CGCCCGGCTA GTATCAGGTC TTTTAAAACA TGTTTTTCCT
74001  CTGGGTTGGT GCTACTAAAT GAATAGCTGA CTTTTCATGG GCTCTTAAAT
74051  TTTTTACATT ATGTTCTTGG ATTTTATTAT TGAGCCAAGA AGGCATCTGT
74101  TTCAACAGGA AATTGCAAGG GGAAAAAAAT TTTTTTTAAA AAAGTAATCT
74151  CTTAGTCTTA CTTGCCAATA AAGAAAACTT TCAGCTGTGC ACGGTGGCTC
74201  ACACCTGTAA TACCAACACT TTGGGAGGCC GAGGTGGGCA GATCACCTGA
74251  GGTCGGGAGT TCGAGACCAG CCTGACCAAC ATGGAGAAAC CCCCATCTCT
74301  ACTAAAAATA CAAAATTAGT CCGGGCGTGG GGGTATACCG CGTGTAAACT
74351  TATTTTCCAT CTATGATGAA AAGTTAAGAA TATTCTGCCC TACAGCATAC
74401  TGTGACTTAT GAAATAAGGA ACAATTGGGG GTTAGGTTAT TGGGCAAATT
74451  GGTCTCTCAT TAAAATATGG TTTCTTTAAC TGGATATAGA AATAAGTTGG
74501  GGACTGCTTT TTTTGGATCT CTAATCCAAA AATCCAAAAC ACTCCAAAAT
74551  TTTGAAACTT TATTGAGGGG CCAACATGAT TGCCACAAGT GGAAAATTCC
74601  ACATCTGGTA TAATGGACAA AAACTTTTCC ATGCACAAAA TTATTTTAAA
74651  ATATTGGGGT AAAATATTTG GGCTATCTGG ATAAGATGTA TATGAAACAC
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FIGURE 3

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74701  AAATGGAATT TTGACTTTGG GTCCCATCCC CAAGATATTC TTCATTATGT
74751  ATATTGAAAA TATTCCCCAA ATCTGGAAAT ATATCCTATT TTTGAAATAC
74801  ATTATGTGTT TCCAAAACCT TGAAACATTT TTTGGGCCCA AACTTTTGGA
74851  TAAGGAATAC TCAACTTTTA ATTTGTTGGG AAGCTTTGTT TTTTAAACAT
74901  TTTTGGGCTG GAAAAAAGCC CCCTGGCCCC AAATTTATCC CTTTGAATGA
74951  ATTGGTTTAT CC
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FEATURES:

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Start: 19364
Exon:          19364-19420
Intron:        19421-34110
Exon:          34111-34143
Intron:        34144-35683
Exon:          35684-35737
Intron:        35738-39940
Exon:          39941-40038
Intron:        40039-45810
Exon:          45811-45871
Intron:        45872-46578
Exon:          46579-46615
Intron:        46616-47002
Exon:          47003-47042
Intron:        47043-47133
Exon:          47134-47184
Intron:        47185-48943
Exon:          48944-49016
Intron:        49017-57568
Exon:          57569-57602
Intron:        57603-57761
Exon:          57762-59835
Stop:          59833
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SNP's:

Position	MMajor	MMinor	Context
3114	G	A	AGGCTGTTTGTTATATGGACCACCAGGTTGGTATTGAATTATTTCTACTCCACCAATAAG ATAAATGAATTAAGGAATTAAAAAAAAAAAGACAATTTTTTTATTTTTATTTTTTTGAGA CACGGTCTCACTCTGTTGCCCAGGCTGTAGTGCAGTGGCACAATCTGGGCTAACTGCAAC CTCTGCCTTCCGGGCTCAAGTGATTCTCCCACCTCAGTCTCCCACGTAGCTGGGACTGCA GGCGTGCATCACCATGTCTGGTTAATTTTTGTATGTTTTGTAGAGAAGCAATTTTGCCAT [G,A] TTGCTCAGGCTATCTCAAACTCCTGGACTCAAGCGATCTGCCCACCTTAGCCTCCCAAAA TGTTGGGATTACAAGCATAAACCACTGCGCCTGGCCATAAGGTGGAAATTTGATGTGGGC AGTTCCAACTTCTCCTCTCTTCAGAGTGAGAATGAGATAGGATATTTATGTCTACTGTTC TTTGAGGCATGCTTAGTGCATTTGTGCCTCACAGTACATTTATCTTAACAGGCCATGTGA TTCTAGTGCAACAGTCCTCAAATTGTGGTTCACAGACCCAGAGGTGCTTTCATGGACTCT
4004	-	A	TCCAGCCTGGCTGACAGAGTGAGACTCCTTCTCAAAAAAAAAAAAAAAAAAAAAAAAATT TTTTATATAAAGCAAATGTACCTATAGCATACTGCTTGACATATGTAGCCCCACAATGAC ACAAAACAAAAAACTAAAATGTTGTTTGGCTCTTCCACTGTGTTGACATTTGTGCTGATG GTGCAAGAGCACCATGGGTAAAATTAAATTACTTGCACTGTAGTGTGAATCAGCATTAGT GGCATGAAACGGTGCTAGTTAGTAGCCATTGCGTTCTTGACTGCCACATACTTGCAGTGT [-,A] AAAAAAAAAAAAAGTCAGTTTCACTATAAAGTCCTTGGTGAAACAGTAAAAATTATTAAT TTTGTTAAATCTTCATCTTTGGGTAATATTTTGTGTTCTTCATGATAAAAGGGAAAATAA ATATAAAGTACTGCTGCATATTGAATAAGATAGTTGTCTTTAGGAAAAGCACTTGTGCAG TTATTTAAGTTGCCAGCTGAATTCATTGCTTTTTATGGAATACTATTTTTGCTTGAATGG ACCATTTACAGATATGCTGTGATTATCAGACTGGTTATTGGTTATTAGTTATTGATTACT
4514	T	G	TTTTTATGGAATACTATTTTTGCTTGAATGGACCATTTACAGATATGCTGTGATTATCAG ACTGGTTATTGGTTATTAGTTATTGATTACTCAAGACTGGTTTTTGGTTATTTGGCGCAC ATTTTTTCCAAAGCGAACAAATTAAGCCTGTCATGTTAAACAACTGACACCATCTATTGC CATTGATAAAATATGAAATGTCAAGTGAAAATTAGAATTTTTAGAAACATATATCTGGCA CTATGTGGTTGAAGCTTTTTCTTTTTTTCTTTTCTTTTCTTTTTTTTTTTTTTGATAAGG [T,G] GTTACTCTGTTACCCAGGCTGGAGTGCAGTGGCGTGATCATCCTGGCTCGCTGCAACTTC TGCCTCTTGGGCTCAGGTGATTCTTCCACCTCAGCCTCCTGAGTAGCTGGTACTACAGGT GTGTGCCACCATGCCAGGCTAATTTTTGTGTTTTTAGTAGAGGCAGGGTTTTGCCATGTT GCCCAGGCTGGTCTTGAATTCCTGGGCTCAAGCAACCCGCCCACCTCAGCCTCCCAAAGT GCTGGGATTACAGGCATGAGCCACAATGTCCAGCCACGGCAGCTTTCTAATATATTAATA

FIGURE 3

Position	MMajor	MMinor	Context
7570	A	G	TAAATGTAAAAGAACCTTTTTCCCTCTCTTAATCTGTAATTGTGACTTGTATGAAGTAGA TACCACAATGAATCAGATGTTAGTTTAACCAATTTTAATAAATAACCTTTCATGGCCGGG TGTGGTGGCTCATGCCTGTAATCCCAGCACTTTGAGAGGCCAAGGTGGGCAGATCACCAG GTCAGGAGATCGAGACCATCTGGCCAACATGGTGAAACCCTGTCTCTACTAAAAATACAA AAATTAGCTGGATGTGGTGGCACATGCCTGTAATCCCAGCTACTGAGGAGGCTGAGGCAC [A,G] AGAATCGCTTGAACCCAGGAGACGTAGGTTGCAGTGAGCCGAGATCACACCACTGCACTC CAGCCTGGCGACAGAGCGAGACTCCGTCTCAATAAATAACCTTTCACTTTAACAAAATGA GAAATGTTACACCAAAATCAAGTCTAACTTTGTCAGCATAATTCTTGCTCTTTAATTTTC ATCTTAATGTTTTAAGCCACAGACTGTTATGTTCTGTTTTCTTAAATGATGGTTGTAGAG GAAAAGAGTAATGCATATAAATTTCCAAATCTACTATCTTAGGTGGTCGTCGGTTTTCTG
11672	C	G	CTGGAGGAAAGGCAGAGTACATAGATGCTTATGATGACAGGTTCTTAGATAGTGCAGGAA CTTGTGGAAGTGTTTTTTTCTGAATGCTTCTGTTTTCTCAGTGAAGTAGAATGCACGTTC AGAATGAAGATAGGGAAGTGTTCTTAGAGATTTGAGGACAAAGGAGAAGGTATAAAGTCA TTATCTATGGAAGTGAGGGATTGGACTAGGGTGCAGGCCAGTAAAACATGGCTTGTGAAC CAAATTCTGCCTGCCCTGTGTTTTTTCGAAACACACAAAGTTTTGTTGTAACCCAAGCATG [C,G] TCATTTATCTGTTGTCTATGGCTGCTTTCCTACTGGAATAGCTGAGTTGAATAGTTACAA CAGAAACCATATGGCTTGCAAAGCATACAGTATTTACTCTCTGGCCCTTTACATAAAAAG TTTGCTGACCTCCAGACTAGGGAAATCTAGTATAATTTCCAGGCAGCCTTAAAAACTCTT TAGAAGTTAATGGTCCAGAATAATGACAAATAGCTGATTGTTGAATTTCACTATCTTCAT TGCCCCTGTTAGAGAGTTTTGAGCTGGAAAGACCGAACTGAACAAAGGATGTCAATGTAT
11897	A	C	ACATGGCTTGTGAACCAAATTCTGCCTGCCCTGTGTTTTTGGAAACACACAAAGTTTTGT TGTAACCCAAGCATGCTCATTTATCTGTTGTCTATGGCTGCTTTCCTACTGGAATAGCTG AGTTGAATAGTTACAACAGAAACCATATGGCTTGCAAAGCATACAGTATTTACTCTCTGG CCCTTTACATAAAAAGTTTGCTGACCTCCAGACTAGGGAAATCTAGTATAATTTCCAGGC AGCCTTAAAAACTCTTTAGAAGTTAATGGTCCAGAATAATGACAAATAGCTGATTGTTGA [A,C] TTTCACTATCTTCATTGCCCCTGTTAGAGAGTTTTGAGCTGGAAAGACCGAACTGAACAA AGGATGTCAATGTATAGGTTTCTTCCACAAATACTGAGCTCTTGCTAGATGCCAGATACT GTGCTAGCCTTGGGAATTCTTGCTCTCAGGAAGCTTACAATGAACTTAAACCTGATTAAA GACAATTCATGAATATATGTGTGATTTCAAATAGAGAACGACATGCCCTATATTGCCTGA CCAAACGGTGCATCATCAAAGTTATTCAAACTGTAGTAGCCTGTGCTGTCTTACTTCTCT
14523	T	C	GATTAAAATTGTAGTTCTTTTTTAACTAGGTGGGACATTCACATCTGGAAACATACTGAA ATTTTTATCTTCTTTTTAGACTTGAAGGCTTTTTTGTTAACATTTTTCGTAAGTTAAAAT ACACTTGATTCAACTACAGTTGCCCTTCCTGTTCAGGTCCTGACATTATCTCTTTTGGAT TATAATACATCTCTATTTTATTTTTTCTTTTGAGACGGAGTCTCACTCTGGCCCAGGCTG GAGTGCAGTGGCATGATCACTGCTCCCTGTAGCCCAGACCTGATCATTTCTCCTTTATCT [T,C] CCAGTAGCTGGGACTATAGGCGTGCGCCACCACACCCAGCTAATTTTTGTATTTTTTGTA GAGACGGGTTTCACCATGTTGTCCAGGCTGGTCTCAAATTCCTGGGCCCGAGTAATCCAC CCACCTGGGCCTCCCAAAATGCTGGGATTACAGGCACAAGCTACCAGGCCTGGCCAGGCA TCTCTTGTGCAGATTTACTTATTCACTAAAGTGATTTGGAAAATAGCCATGTGTGCAAGG TTTACAAAAATAACTTACCTAGTTTCACTGTAGCTTTCTAAACAAGTTTTGAAACTTTGT
16586	C	T	AGCTTCACATTTATTCCATAGAATTATATTGTTTTTCTTATAATGAACATATAATTCATA TGTGATATATAGCAGTCATGTTGTTTTATTCTCTACAGGTATGTTCGCAATTCGTGCTGA TCATGATTTTGTAGTACAGGAAGACTTCATGAAAGCAGTCAGAAAAGTGGCTGATTCTAA GAAGCTGGAGTCTAAATTGGACTACAAACCTGTGTAATTTACTGTAAGATTTTTGATGGC TGCATGACAGATGTTGGCTTATTGTAAAAATAAAGTTAAAGAAAATAATGTATGTATTGG [C,T] AATGATGTCATTAAAAGTATATGAATAAAAATATGAGTAACATCATAAAAATTAGTAATT CAACTTTTAAGATACAGAAGAAATTTGTATGTTTGTTAAAGTTGCATTTATTGCAGCAAG TTACAAAGGGAAAGTGTTGAAGCTTTTCATATTTGCTGCGTGAGCATTTTGTAAAATATT GAAAGTGGTTTGAGATAGTGGTATAAGAAAGCATTTCTTATGACTTATTTTGTATCATTT GTTTTCCTCATCTAAAAAGTTGAATAAAATCTGTTTGATTCAGTTCTCCTACATATATAT
16644	T	C	TATGTGATATATAGCAGTCATGTTGTTTTATTCTCTACAGGTATGTTCGCAATTCGTGCT GATCATGATTTTGTAGTACAGGAAGACTTCATGAAAGCAGTCAGAAAAGTGGCTGATTCT AAGAAGCTGGAGTCTAAATTGGACTACAAACCTGTGTAATTTACTGTAAGATTTTTGATG GCTGCATGACAGATGTTGGCTTATTGTAAAAATAAAGTTAAAGAAAATAATGTATGTATT GGCAATGATGTCATTAAAAGTATATGAATAAAAATATGAGTAACATCATAAAAATTAGTA [T,C,A] TTCAACTTTTAAGATACAGAAGAAATTTGTATGTTTGTTAAAGTTGCATTTATTGCAGCA AGTTACAAAGGGAAAGTGTTGAAGCTTTTCATATTTGCTGCGTGAGCATTTTGTAAAATA TTGAAAGTGGTTTGAGATAGTGGTATAAGAAAGCATTTCTTATGACTTATTTTGTATCAT TTGTTTTCCTCATCTAAAAAGTTGAATAAAATCTGTTTGATTCAGTTCTCCTACATATAT ATTCTTGTCTTTTCTGAGTATATTTACTGTGGTCCTTTAGGTTCTTTAGCAAGTAAACTA

FIGURE 3

Position	MMajor	MMinor	Context
17969	A	G	AATAGAAAATGGAGTGGTCAAGTTAGCCATCTCATACTCAAAATTATTGTACAGTTCTAT TTCTATGTGTTGGCAGTGCATTTTATGTGACAAAAAGTAGAATGTAGGGGGAGGTTTAAG TCAAATATCTATGTGATCTTTTCACTTATAATTTGCATTTAGTTAAGGAGTGACTATCTT GCCTTTTACCTTTGTGCTGGCGGTGGTTTTTTTAAAGAATCAATTTGGTGTACAAATCCTT TCTTTCTTTTTTTATTTTTGATTTTTTTTTGAGATGGAGTTTCGCTCTTGTTGCCCAGGCT [A,G] TAGTGCCATTGCACTATCTCAGCTCATTGCAACCTCCGCCTCCCGGATTTAAGCGGTTCT CCTGCCTCAGCCTTCTAAGTAGCTGCGATTACTGGCATGCGCCACCACACCCAGCTAATT TTTGTATTTTTAGTAGAGACGGGGTTTTTCCATGTTGGTCAGGCTGGTCTCAAACTCCCG ACCTCAGGTGATCCACACGCCTCAGCCGCCCAAAGTGCTGGGATTACAGGCGTGAGCCTC CGCGCCCGGCCCAAATCTTTTCACCATGGGTTTACAGGCATAACGCCACCACACCCAGGG
18117	C	T	TAATTTGCATTTAGTTAAGGAGTGACTATCTTGCCTTTTACCTTTGTGCTGGCGGTGGTT TTTTAAAGAATCAATTTGGTGTACAAATCCTTTCTTTCTTTTTTTATTTTTGATTTTTTT TGAGATGGAGTTTCGCTCTTGTTGCCCAGGCTATAGTGCCATTGCACTATCTCAGCTCAT TGCAACCTCCGCCTCCCGGATTTAAGCGGTTCTCCTGCCTCAGCCTTCTAAGTAGCTGCG ATTACTGGCATGCGCCACCACACCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTT [C,T] TCCATGTTGGTCAGGCTGGTCTCAAACTCCCGACCTCAGGTGATCCACACGCCTCAGCCG CCCAAAGTGCTGGGATTACAGGCGTGAGCCTCCGCGCCCGGCCCAAATCTTTTCACCATG GGTTTACAGGCATAACGCCACCACACCCAGGGAATTTTAAAATTGTTTTTTAGAGAGGGG GGTCTTACTATTTTGCTCAGGCTGGCAAACTCCTTTTAAAAGATATTGAAAGCCATCTGG TTTATTATTTTTATTTCAAAATATAATAATGGAAGAAATTTTACAGTATTATATACAATT
18518	C	A	GCCCAAATCTTTTCACCATGGGTTTACAGGCATAACGCCACCACACCCAGGGAATTTTAA AATTGTTTTTTAGAGAGGGGGGTCTTACTATTTTGCTCAGGCTGGCAAACTCCTTTTAAA AGATATTGAAAGCCATCTGGTTTATTATTTTTATTTCAAAATATAATAATGGAAGAAATT TTACAGTATTATATACAATTTACTGAGTCAGCTATCAGTTCCTTTTTCTGATTTTTTTCT AGTTGCCATTCTTGATATTTTCTAGGTAATCTAAACTGAGTTGTATTTTCAAGTACTCTT [C,A] AAATACTTTAAAAAATTTTAAATTGAGCCGTTTAATTCTTTGCTTAAAGGTGATGGGTAT TTTATTTTCTGTATGGCACCACGTGATTTTAAATTGAACTCTTCATTTATTAGTCATTTG GTTATAAACTCAGCATAGATTGCGCAGAATTTTGAGAGGGGAGAAACTATAGCTTTCCTT TCGGATGCCACTGGTGGGTAGCCTGTTTTGCCTGTTTGTTCTTATGTTAAAGAAGGGCTC TACGTCCTGTCTGGAAAGGGCGGAGCTGGCTCGGACCGCCCCACTGCCTTTCCCAGGACC
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20999	-	T	ACTTTGTTTGTGACTATCACTGTTGCAAAATGTAGTGCAGTGGTGTGATCTCGGTTCACT GCAGTCTCGAACTCCCATGCTCAAGCCATCCTTTCACCTCAGCCTCTGGAGTAGCTGGGA CCATGCCGGGCTAATTTTTCTTTTTTTTTTTTTTGTAGCGATGGGTTTTTTCTCCAGGCT GGTCTCGAACTCTTGGCCTCAAGATCCTCCCGCCTTGTCCTCCGAAAGTGTTGGGATTAC AGGTGTGAGCCACTGCACCTGGCCCAAGAATATACTCATGGTTTTTTTGTTTTTTTTTTT [-,T] TTTTGACACAGAGTTTCACTCTTGTTGCCCCAGGCTGGAGTGCAGTGGCGCTGTCTCAGC CCACCGCAGCCTCTGCCTCGGGTCCCGGTTCAAACAGTTCTCCTGCCTAAGCCTCCTGAG TAGCTGGGGATTACAGGCGCGCACCGCCAGGCCCAGCTTTTTTTTTTTTTTTTTTGAG ACAGAGTCTCACTCTGTCGCCCAGGCTGGAATGATCTTGCAGTGGTGCGATCTGGGCTCA CTGCAAGCTCTGCCTCCCGTGTTCACGCCATTCTCCCGCCTCAGCCTCCCGAGTAGCTGG

FIGURE 3

Position	MMajor	MMinor	Context
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21625	C	T	GGGCTAATTTTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATATTGGCCAGGATGGTC TCAAACTCCTGACCTTGTGATCCGCCTGGCTTGGCCTCCCAAAGTGCAGGGATTACAGGC GTGAGCTACCGCGCCCGGCCAATATACTCTTAGAAAACAGGAGGTCATATTTAGGCTAGT TATAAAAATGAATTTATACTTAACATACAATAATGTGAATGAAGAGTATGCTTTTATTTA TTTATTTATTTTTTTTGAGACGGAGTTTCACTCTTGTTGCCCAGGCTGGAATGCAGTGGCG [C,T] GATCTCCGCTCACTGCAACCTCCGCCTCCCACGTTCAAAAGATTCTCCTGCCTCAGCCGC CTGAGTAGCTGGGATTACAGGCGCCCGCCACCACTCCCGTCTAATTTTTGTACTTTTAGT AGAGACGGGGTTTCACCATGTTGGCCCTGCTGGTCTGGAACGCCAGACCTCAAGTGATCC GCCTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCTTGAGCCACCGCGAAGGAGTATG CTTTCATATCCTCAAAATGATTCAGTAATTTCAGCACTTAACTGCAAGCAACCTTACAAA
26291	C	T	ATTTTAGTATTGTGTATATAGGATTCAGCACTATCCTCAAATGTATGAACATATCCCCTG TGGATAAGGGGGGACTACTGTATTTGTAAAAGTTCATATTTCATATTTCAATGCATATAA GAATTATTTTATCTAATGGTTACAGTCTATATCCTTCATTGATGTGTTTATTTGAGGGTC TTTGAACATTTTTGTAACTTTTCTCTATCCAAATGCAGTTTTATAGATCATTTTTATGGA AAGGAAGGAGATAATTCGGAAGGATGTTTTAACATGTGGTACTTTCTACCTCATGTTGAT [C,T] GAAAGATTTTCACTTGTGAATTAATTTGTCTCAGAATCATGGTGTTTCACAATAGAGGGT TATTTTGGTTTATCTGGCTTGCCTTGGTTTGGTTAATGTGGTTGAACTGCTTGGCTACTC ATAAAGTTTGGGAAATTGATTTCTACTAATTAATTACAATAGTAACTTAAAATAGATCAT TGCTGGTGATATGGAGATGCCTCCATTAATACCACGGTTTCTAAAATGATAGATTTCAGG AGTAGTGTGAGCAGGCTGAGATTAAGAATTAAGTGTGATAGTGGCAAGACTTGGTTATTA
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28030	T	G	ACAAACTGACACAAAGTATCATCTATTATTATTCTAAGGGCCCATTTATCTTTCTCCAGA ATTGTTCTTCTAAATTGCCTGTATACCTCTACCCCCATGCTATATAAAGGGTATATAAAC TCCTAAATATCACTTTTTTTTTTTTTGTATACACGTTTCTTTCCTGTGATACCCCCATGC ACATAATGAATCTGTATACCTTTTCTCCGTTTAGTTTATTTCATAGACTGGTTTGAAATA TCACGGATTTTGTTTGTTTTTGGTATACACTTTTTAAAAATATCACTTTTTTTTTTTTGG [T,G] ATACACTTTTCTTTCCTGTGATACTCCCATACACATAATAAATTTGTATACATTTTCTCC ATTTAGTTTATTTCATAGACTGTTATCGAATCCTGATGGTAGAGGGAAAGTCTTCCTTGC CTTACACAAGTATTTCCCAGAATATATTTACACCATTCCTTGATATGTGTTGCCCTGTTT TTTTTTCTTTAATTACACAAAATTTAGTGATTTCACTTTAGATAAATTCAAAAGTACGCA TTTCTTTAATTGATTTTCTTCTTTATCACAGCTCTGACAAGTTGCTTCAGGAAGATAAGG
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FIGURE 3

37703	A	G	CCATTATCTAAAAACAACAACAAAAAATAATAATGGAGATAAACCTAAATGGATAAACTC CTTTTTAAACACTCATTTACTGTTATTATTTTGTGGGAGAGGAGTGGGGTCTTGCTCTGT TACCCAGGCTGGAGTACAGTGGCGCGCTCTCATAGCTCACTGTAACCTCAAACTCCTGGG CTCAAGCTGTCTTCCCACCTTAGTCTCCCAAGTAGCCAGGACTACGGGCACACACCACCA TGCCTGGCTTAATTCTCAAAGTTTTTGTAGAGATGGAGTCTGGCTATGCTGGCCACATTT [A,G] CTTAAGTATATCTTTTTATTAAATTCAAATACAGTTTAAATAAAAGGGACAAATTTAGGG CCTTTGTAATTAGTAAACGGTTTGTTTTTGTAAAGTTTTTCTACTGTTTTTAAATGTGAG GTAAGGTCATAATTTGCTTCATATTAGGTTGGTGCAAAAGTAATTGCAGATCTGCCTCTG AAAAGTACAAAATCTATTCGCTGTTACGTTAGGGCTCTATTTTGATAGTTTATTTTTATT TAGTAGTAGTCTATTGGGCCTTCAAAACTTGTTTAAGCATATTTATACATAATTATGTGC
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POSITION	Allele 1	Allele 2	
3114	G	A	Beyond ORF (5')
4004	-	A	Beyond ORF (5')
4514	T	G	Beyond ORF (5')
7570	A	G	Beyond ORF (5')
11672	C	G	Beyond ORF (5')
11897	A	C	Beyond ORF (5')
14523	T	C	Beyond ORF (5')
16586	C	T	Beyond ORF (5')
16644	T	C	Beyond ORF (5')
17969	A	G	Beyond ORF (5')
18117	C	T	Beyond ORF (5')
18518	C	A	Beyond ORF (5')
19882	G	A	Intron
20988	G	-	Intron
20999	-	T	Intron
21465	A	G	Intron
21625	C	T	Intron
26291	C	T	Intron
28012	T	C	Intron
28030	T	G	Intron
33671	A	C	Intron
37703	A	G	Intron
39269	C	G	Intron

Map:
Bac accession number: AL139317.2
Human chromosome 14

FIGURE 3

SEQUENCE LISTING

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Sanders, Robert D.
Gilbert, Dennis A.
Beasley, Ellen
Bonazzi, Vivien R.

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